THE UPPER OESOPHAGEAL SPHINCTER

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We shall not cease from exploration
And the end of all our exploring
Will be to arrive where we started
And know the place for the first time

T S Eliot

DECLARATION

The work described in this thesis has been conducted with the assistance and advice of those acknowledged on page iv.

I certify that this thesis has been composed by me alone.

ABSTRACT OF THESIS

The initial aim of the study was to establish a reliable system for analysis of upper oesophageal sphincter (UOS) motility using a computerised waveform analysis system and a 6 sensor strain gauge assembly. The fidelity of the computer recorder was confirmed by sequential or simultaneous recording with a conventional chart recorder in 50 subjects. Simultaneous digital and analogue recording showed variation of 2 to 9%. The strain gauge assembly was evaluated by comparison with a conventional 4.7 mm diameter multilumen perfused manometric catheter in 23 subjects. Measurements of UOS pressures were more susceptible to changes in catheter diameter and orientation than those of the oesophageal body and lower oesophageal sphincter. The strain gauge assembly thus appears to record more physiological UOS pressures due to its narrow diameter and circumferential pressure sampling. Pharyngeal contraction amplitudes were significantly greater when recorded by strain gauges than by perfused side-holes, due to the much greater frequency response of the intraluminal transducers.

A study of normal pharyngo-oesophageal (P-O) motility was then performed in 67 healthy volunteers. The strain gauge assembly was compared with a modified sleeve sensor and with the perfused side-holes of the sleeve catheter in 50 subjects. Biological variation was also assessed by performing repeat studies in 15 volunteers. A considerable methodological variability was demonstrated between the two catheters, both in tonic UOS pressure measurements and in water swallow patterns. Male subjects had a greater axial asymmetry than females and there was a significant increase in UOS wet swallow after-contraction in females. The effect of bolus consistency on P-O motility was also assessed and significant temporal and pressure differences in swallow patterns demonstrated. Increasing age was associated with reduction in peristaltic amplitude, tonic UOS pressure, duration of pharyngeal and upper oesophageal waves and with an increase in pharyngeal contraction amplitude.

Having established the normal values for P-O motility and their variation, a series of clinical investigations was performed. The association of gastro-oesophageal reflux and UOS function was studied by prolonged pH monitoring in 98 subjects and by infusion of the upper oesophagus with 0.1N HCl. No positive association of acute or chronic acid exposure was found with any parameter of pharyngo-oesophageal motility. The possible association of reflux and posterior laryngitis was assessed by pH monitoring and distal oesophageal and posterior laryngeal biopsies in 87 patients, of whom only 17% were found to have reflux-associated laryngeal changes.

The aetiology of globus sensation was explored in 207 patients attending a special clinic. Gastro-oesophageal reflux was assessed by pH monitoring (87) and by distal oesophageal biopsy (107) and was found to be abnormal in under 30% of patients, compared with previous estimates of up to 90%. Detailed assessment of P-O motility was compared in 75 further globus patients and 67 controls. Regression analysis with age and sex showed an abnormal wet swallow pattern, comprising an increase in upper sphincter after-contraction pressure, increased pharyngeal contraction and a reduced swallow complex duration. Psychometric evaluation of 167 patients showed that males were similar to controls but female patients were introverted and had an increased incidence of occult psychiatric morbidity and of depression, anxiety and somatic concern. Aetiological factors identified, therefore, include hypertonic, rapid swallow patterns and, in females, mild affective disturbance and heightened awareness of bodily sensation.

P-O motility was also assessed in 1) 19 patients following irradiation for laryngeal carcinoma who showed a significant reduction in P-O wave velocity, 2) 33 patients with otherwise unexplained cervical dysphagia who showed no significant differences from age-matched controls and 3) 14 patients with dysphagia of neurological origin, who showed reduction in UOS contraction amplitudes and, where a vocal cord palsy was present, a trend to reduced UOS tone.

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LIST OF ABBREVIATIONS USED IN THE TEXT

AET	acid exposure time
ant	anterior
cAMP	adenosine 3', 5' - cyclic monophosphate
CCEI	Crown Crisp Experiential Index
cGMP	guanosine 3', 5' - cyclic monophosphate
CI	confidence interval
cm	centimetre
CR	coefficient of repeatability
CV	coefficient of variation
diff	difference
EMG	electromyography
ENT	ear, nose and throat
EPI	Eysenck Personality Inventory
EPQ	Eysenck Personality Questionnaire
F	female
GHQ	General Health Questionnaire
GOR	gastro-oesophageal reflux
GR800	Gaeltec computerised recorder
H_2O	water
HCl	hydrochloric acid
HOQ	Hysteroid Obsessoid Questionnaire
IBM	International Business Machines
KCl	potassium chloride
KHz	kilohertz
LOS	lower oesophageal sphincter
M	male
ml	millilitres
mm	millimetres
mmHg	millimetres of mercury
n	number of subjects
$NaHCO_3$	sodium bicarbonate
no	number
NS	not significant
%	per cent

p	probability
post	posterior
r	Pearson correlation coefficient
RPT	rapid pull-through
r_s	Spearman correlation coefficient
SD	standard deviation
sec	second
SEM	standard error of the mean
SPSSX	Statistical Package for Social Sciences
SPT	station pull-through
UOS	upper oesophageal sphincter
URTI	upper respiratory tract infection
VIP	vasoactive intestinal polypeptide
X	mean
X^2	chi-square

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PART I: HISTORICAL PERSPECTIVE

1. INTRODUCTION

1.1 ANATOMY OF THE PHARYNGO-OESOPHAGEAL JUNCTION

'The cricopharyngeal sphincter is a kind of no-man's land lying between the region of the laryngologist above and that of the thoracic surgeon below' - Lund 1965a.

The pharynx is suspended from the base of the skull and the medial pterygoid plates by the pharyngo-basilar fascia (Last 1978). Anteriorly, the pharynx communicates with the nose (naso-pharynx), oral cavity (oropharynx) and the larynx (laryngo- or hypopharynx). Its walls comprise 3 overlapping muscular constrictors. The superior constrictor overlaps the pharyngo-basilar fascia, sharing its origin from the medial pterygoid plate but also arising inferiorly from the pterygomandibular raphe, down to the level of the posterior border of the last lower molar tooth. Posteriorly, its fibres fan upwards to the pharyngeal tubercule of the basiocciput and downwards to join the posterior median pharyngeal raphe, extending to the level of the vocal cords. The middle constrictor arises from the lower stylo-hyoid ligament and the greater cornu of the hyoid. The middle constrictor overlaps the superior constrictor and is itself over-lapped by the upper fibres of the inferior constrictor in its insertion to the posterior raphe down to the level of the vocal cords. Below this level, the posterior wall comprises only the thin fibres of the thyropharyngeus muscle, the upper part of the inferior constrictor which arises from the oblique line of the thyroid cartilage. Inferiorly is the cricopharyngeus muscle, so named by Valsalva (1707, not 1717 as is cited almost universally) who also recognised it as the upper oesophageal sphincter. The upper 'pars obliqua' is contiguous with the lower fibres of the thyropharyngeus and is inserted into the posterior raphe. The lowermost fibres or 'pars fundiformis' (Killian 1908) constitute what is by convention regarded as the cricopharyngeus proper (Goyal and Cobb 1981) and sweep round from one side of the cricoid arch to the other without median insertion. The area of the pharyngeal wall between the inferior border of the middle constrictor and the upper border of the pars fundiformis of the cricopharyngeus muscle is commonly termed Killian's dehiscence and is the recognised site of protrusion of pharyngeal pulsion diverticulum (Keith 1910). Lund (1965a) suggests, however, that the term 'dehiscence' is a misnomer as the muscular sheet is continuous.

The four major orifices of the pharynx are protected from the passage of food by a sphincteric mechanism. Contraction of the horizontal fibres of the palatopharyngeus (Passavant 1869) form a ridge at the inferior free margin of the pharyngo-basilar fascia, at the level of the hard palate, against which the soft palate is elevated by the levator palati muscles. The levator palati muscle arises from the apex of the petrous temporal bone and adjacent cartilage of the Eustachian tube and is inserted into the nasal surface of the aponeurosis of the soft palate. The palatopharyngeus muscle arises from both the hard and the soft palate, sweeps laterally to the tonsil, the upper part raising the posterior palatine fold of the fauces and the lower part being inserted into the thyroid cartilage. Some of the lateral fibres sweep round medial to the superior constrictor, forming a horizontal U-shaped sling, embracing the vertical V-shaped insertion of the levator palati muscles in closure of the nasopharynx. The palatoglossus muscle arises from the undersurface of the soft palate and passes downwards to interdigitate with styloglossus, thus raising the anterior faucial fold. It has a sphincteric action at the oropharyngeal inlet: contraction elevates the tongue and narrows the transverse diameter of the fauces. Anterior to this, the action of the mylohyoid in elevating the tongue further protects the oral cavity.

At the level of the hypopharynx, the upper aerodigestive tract divides into separate channels for respiration and deglutition. The powerful inlet sphincter of the larynx protects against ingress of food into the lower airways, and is supplemented by vocal cord apposition and the backward tilt of the epiglottis. The inlet sphincter is formed by the action of the aryepiglottic muscles which lie in the upper free edge of the quadrate membrane. The sphincter is active only during deglutition and the action of the aryepiglottic muscles, which run between the lateral aspect of the epiglottis and the posterior surface of the contralateral arytenoid, is to draw the arytenoids together and the epiglottis downwards.

The vocal cords are approximated by the lateral cricoarytenoid and the interarytenoid muscles. Upward movement of the larynx during swallowing has important implications for manometric study because of potential measurement artifacts (Levitt et al 1965). The larynx rises before hyoid elevation occurs, and is drawn upwards by stylopharyngeus, assisted by salpingo- and palatopharyngeus. The laryngopharynx is thus drawn upwards over a bolus which 'cannot retreat' because of the oropharyngeal and nasopharyngeal closure (Negus 1950, Palmer et al 1988). Upward laryngeal movement also appears to cause active folding of the epiglottis which supplements the pull of the aryepiglottic muscles and the passive tilt of bolus passage. Forward hyoid movement with gross shortening of the thyrohyoid fold causes extreme forward tension on the hyoepiglottic ligament at its attachment to the margins of the epiglottic tubercle. The tubercle thus bulges backwards transversely as well as craniocaudally (Fink and Demarest 1978).

At rest, the oesophageal inlet is protected principally by the sling-like horizontal fibres of cricopharyngeus, to prevent air entry during respiration (Negus 1925). Below the cricoid, the longitudinal muscle fibres of the cervical oesophagus diverge into two lateral bands, leaving a triangular posterior deficiency in the longitudinal layer known eponymously as the Killian-Jamieson area (Zaino et al 1967). The two lateral bands meet anteriorly on the posterior surface of the cricoid in a stout tendon, while the circular fibres of the cervical oesophagus blend with the lowest fibres of the inferior constrictor (Birmingham 1899). In the anterolateral area below the horizontal fibres of cricopharyngeus is another weak area corresponding to the entry of the recurrent laryngeal nerve which can be a site of mucosal protrusion (Ekberg and Nylander 1983). The first report of excision of pharyngeal diverticulum was of a congenital pharyngocele in a four year old girl (Nicoladoni 1877). Acquired pharyngoceles have a male preponderance and protrude through either of two weaknesses in the lateral pharyngeal wall. The upper dehiscence occurs between the superior and middle constrictors and is in relation to the lower pole of the tonsil. Such pouches may be self-induced in criminals wishing to conceal small stolen objects (Norris 1979). The lower weakness is deep to the thyrohyoid membrane, between the middle and inferior constrictors, posterior to the thyrohyoid muscle and corresponding to the entry of the superior laryngeal nerve (Komisar 1983). Increase in turgidity of the ventral and dorsal pharyngolaryngeal venous plexi may assist prevention of air entry during inspiration (Tose et al 1984). The separation of the ventral plexus into two postcricoid plexi, each 2 cm wide, may assist separation of the two lateral food channels, particularly important at the interarytenoid level where the wall surrounding the glottis is low (Pitman and Fraser 1965).

The manometric upper high pressure zone is consistently found to be 2 - 4 cm in length (Fyke and Code 1955, Atkinson et al 1957, Sokol et al 1966, Goyal et al 1970), ie more than twice the length of the cricopharyngeus (Code and Schlegel 1968). Early observers considered the upper circular fibres of the oesophagus to participate in the sphincter (Killian 1907, Keith 1910). At oesophagoscopy, the relatively slight dilation of the cervical oesophagus compared with the thoracic oesophagus, has also been taken as indirect evidence that the cervical oesophagus contributes to the high pressure zone (Clerf and Putney 1942). Zaino et al (1967) considered the radiological upper high pressure zone to be below the lower pole of the cricoid, and identified, during anatomical dissection, coarse circular fibres in the upper part of the oesophagus which were believed to comprise the true UOS. In contrast, electromyographic studies indicate that, in the opossum, the cricopharyngeus and adjacent fibres of the inferior constrictor discharge continuously at rest, but not the musculature of the upper oesophagus (Asoh and Goyal 1978). While studies in man have shown spontaneous resting discharge from the cricopharyngeus (Hellemans et al 1970, Shipp et al 1970), there is only indirect radiological evidence that in man, as in the opossum, the inferior constrictor adjacent to the cricopharyngeus contributes to the observed high pressure zone (Goyal and Cobb 1981). Manometric studies continue to indicate that the length of the maximum tonic pressure zone is 1 cm (Kahrilas et al 1988a).

1.2 COMPARATIVE ANATOMY

'The adaptation of the organism to the nutritional opportunities of its environment is an elementary necessity of each species' - Bosma 1957.

Vertebrates prepare food for swallowing in a variety of ways. The primitive engulfing action by which the snake employs its teeth to hold its prey intact while its body progresses over it (Negus 1949) has some counterpart in the upward motion of the human pharynx (Mendelsohn and McConnel 1987). Birds, which lack tongues, require to jerk their heads forwards to engulf large pieces of food (Miller 1982). A similar action has been observed in humans following pharyngeal paralysis (Bosma 1957). Other animals, such as the pig, employ extra-oral division of food.

With the exception of the lung fish, Lepidosteus, which has a posteriorly placed pneumatic duct, the respiratory channels enter the anterior aspect of the pharynx (Bosma 1957). In man, unlike lizards, tortoises or birds for example, the presence of a large larynx is a potential impediment to deglutition and there is also the additional problem in humans of nasopharyngeal closure during swallowing (Negus 1949). In lower vertebrates, including reptiles and birds, the epiglottis is vestigial or absent (Miller 1982) and its absence in man causes little or no handicap (Negus 1949). The corniculate cartilages are also present only in mammals. The epiglottis is essentially a mammalian structure. In mammals relying heavily on olfaction (eg deer, cow, tiger, dog) it is large and extends intranasally to prevent the interruption of respiration during swallowing. The epiglottis is also retrovelar in monkeys and other non-human primates. In such species the intranarial larynx is clasped by a well-developed palatopharyngeus. In those animals swallowing large amounts of liquid food (eg whales, ruminants) there are well-developed side-walls rising above the glottis (Last 1978). In man, the arytenoids are small and the aryepiglottic folds are, therefore, reinforced by the presence of the cuneiform cartilages of Wrisberg. These folds, perhaps assisted by the lateral ventral pharyngeal venous plexi, are remnants of the lateral walls protecting the glottis (Bowles 1889) but well-developed food channels are lacking.

In man, the larynx at birth lies opposite the second to fourth cervical vertebrae and descends by puberty to its adult position opposite the sixth cervical vertebra (Cowan 1982). The descent of the human larynx is due to the erect posture and the recession of the jaws. The extranarial site of the human larynx requires interruption of the respiratory cycle during swallowing. The thyrohyoid separation which occurs in man may be a modification for vowel production during speech (Fink and Demarest 1978). In apes, the thyroid cartilage isthmus adjoins the body of the hyoid, while in monkeys the two structures overlap with an intervening median air sac. Non-primates have a hyoepiglottic muscle rather than a ligament and the median thyrohyoid fold does not develop. In animals with an intranasal larynx, the vallecular base of the epiglottis impinges on the soft palate during swallowing and it is this pressure which flips the epiglottis backwards. Although the human larynx also must be elevated to produce epiglottic inversion, the specialised folding of the epiglottis by the aryepiglottic muscles and the pull of the hyoepiglottic ligament allows the elevation to stop short of the soft palate while still protecting the laryngeal inlet. The relative mobility of the human soft palate is also an adaptation for vocalisation (Bowles 1889).

In most animals which use their forelimbs merely for locomotion, the larynx is not of a mechanical valvular type. The reindeer, for example, cannot close its larynx completely (Negus 1950). In man and other animals of arboreal descent, the forelimbs are frequently used in powerful manoeuvres, and the larynx consequently has a valvular mechanism of glottic closure to fix the volume of air in the thorax and prevent air entry during pectoral movements. Negus also postulated that the cricopharyngeal sphincter is correspondingly more active in man to prevent air being sucked into the oesophagus under these circumstances. In four-footed animals the mouth and feet are also well-placed for the vital functions of seeking out food, digging for it, catching and carrying. In the erect posture these functions are taken over by the forelimbs. The altered quality of the human diet from raw foodstuffs to cooked and refined foods eaten with implements has also produced dental disease, loss of teeth and altered demands on the previously stable patterns of mandibular muscle activity (Thomson 1982).

In most mammals, the pharyngeal constrictors are transverse but the laryngeal descent in man results in obliquity of the constrictor fibres which are tethered to the basi-occiput by the posterior median raphe and are thus unable to move inferiorly (Negus 1950). When the larynx rises during swallowing, however, the fibres become almost transverse. The infantile triad of omega-shaped epiglottis, situated almost transversely and with close approximation of the thyroid cartilages to the hyoid bone, reappears transiently during swallowing (Fink and Demarest 1978) suggesting that infantile laryngeal morphology constitutes a partial protective closure of the larynx. Following laryngectomy, the constriction caused by the upper oesophageal sphincter can vibrate in the production of oesophageal speech - Gurnards ('crooner' fish) possess a similar mechanism with a sphincter at the mouth of their air sacs.

The posterolateral walls of the pharynx show less interspecies variation (Sprague 1944) but in monotremes the stylopharyngeus muscles meet anteriorly to form a primitive anterior pharyngeal constrictor. In marsupials, additional dilator fibres to the lateral walls of the phayrnx develop and in placental mammals there are no stylopharyngeus constrictor fibres but a superior pharyneal constrictor is present. The more primitive species also possess well developed palatopharyngeal folds which meet posteriorly in a median dorsal fold. In mammals, the folds are less well developed but the levator palati is developed from the anterior end of palatopharyngeus which represents the longitudinal part of the primitive posterior constrictor of the pharynx (Edgeworth 1916). In the cat, instead of a simple sphincteric arrangement, there is a prominent mucosal fold forming a downwards funnel (Bosma 1957). In the pig there is a tendency for pharyngeal mucosa to herniate through some of the constrictor fibres although the efficient palatopharyngeus in this animal tends to keep food in the lateral channels (Bowles 1889, Negus 1938). In man, there is no such mechanism to prevent the bolus being forced against the weak area just superior to the cricopharyngeus. Comparison of cat, dog and monkey reveals all of these species have a large mouth and tongue connected by a restricted faucial isthmus to a spacious pharynx. The most distinctive difference is the greater prominence of the levator palati and palatopharyngeus muscles in the monkey (Miller 1982). Also, carnivores have glands producing mucus at the pharyngo-oesophageal junction, unlike herbivores and omnivores.

Carnivores possess a short, radially distensible pharynx, but elongation and descent of the human larynx causes the pharynx to descend with its sling-like suspension to lie within an enclosure of muscles of spinal segmental origin (Bosma 1957). An electromyographic study of dogs, cats and monkeys indicated that the 'lead complex' of swallowing in all three species included two of the sling suspension muscles - palatopharyngeus and stylohyoid - as well as the superior constrictor extrinsic and posterior intrinsic tongue musculature (Doty and Bosma 1956).

With increasing laryngeal specialisation, there is also a convergence of extrinsic pharyngeal suspensory musculature upon the laryngeal cartilages, so that stylopharyngeus inserts primarily into the tongue, hyoid and larynx. In man, palatopharyngeus is partly inserted into the posterolateral thyroid cartilage, and the pharynx is large compared with other primates, for purposes of phonation (Negus 1950). Negus (1950) also describes in man the attachment of the anterior wall of the oesophagus to the corniculate cartilages of Santorini, providing a mechanism of oesophageal opening as the larynx moves upwards and forwards on deglutition although the corniculate cartilages in man are rarely prominent (Fishman 1935). In the dog, there are additional fibres linking the longitudinal muscle coat of the oesophagus to the thyro-arytenoid muscle.

In humans, the upper one third of the oesophagus is striated and there is a transition zone where smooth and striated muscle fibres mingle and the myenteric plexus and muscularis mucosae are said to originate (Zaino et al 1967). The opossum oesophagus has a similar muscle pattern to humans and monkeys while dogs, cats and rodents have striated muscle throughout the length of the oesophagus (Christensen 1983) and the pigeon has smooth muscle in the upper oesophagus (Postorino et al 1984)

Species differences of innervation will be considered in Section 1.3

1.3 INNERVATION OF THE PHARYNGO-OESOPHAGEAL SEGMENT

'Swallowing is probably the most complex reflex which can be reproducibly elicited by stimulation of a peripheral nerve' - Doty et al 1967.

1.3.1 Efferent Supply of the Laryngopharyngeal Musculature

The motor nerves supplying the laryngopharyngeal musculature concerned with swallowing are the trigeminal (mylohyoid, muscles of mastication, tensor palati, anterior belly of digastric), facial (stylohyoid, posterior belly of digastric), glossopharyngeal (stylopharyngeus), vagus (levator palati, palatopharyngeus, salpingopharyngeus, arytenoid muscles) and hypoglossal (thyrohyoid and geniohyoid). In addition, some fibres of the spinal accessory nerve are distributed via the vagus (Christensen 1987). The vagus, glossopharyngeal and spinal accessory nerves form the motor input to the pharyngeal plexus and were known collectively in early works as the 'eighth pair' of nerves (Reid 1838). Many of the motor fibres are not general visceral (autonomic) efferents but special visceral efferents to the striated musculature (Weisbrodt 1976). Vagal and sympathetic autonomic fibres innervate the pharyngeal glands and vessels. Ganglionated plexi of unknown function are found in the pharynx: they are not concerned with striated muscle function and may be sensory. The nerve fibre: muscle cell ratio in the rabbit pharynx is 1:2 to 1:6 - compared to 1:2,000 for human gastrocnemius. The vagal fibres innervating motor end plates are cholinergic nerves whose release of acetyl choline stimulates nicotine receptors like those of somatic muscle elsewhere (Christensen 1983). No overlap of motor units has been demonstrated.

The cricopharyngeus muscle is innervated by the vagus whose pharyngeal motor branches were described by Reid (1838). Reid observed palatopharyngeal paresis after experimental section of the pharyngeal branch of the canine vagus. The later suggestion

(Negus 1949) that tonic activity of the UOS was sympathetic (adrenergic) appeared intrinsically unphysiological (Doty 1968) and was disproved by the findings of Lund (1965a) that sympathetic stimulation of the isolated dog UOS produced no alteration in sphincter tone. Subsequent EMG investigation in dogs also confirmed the absence of sympathetic motor supply (Levitt et al 1965). Nonetheless experiments in cats using both EMG (Murakami et al 1973) and intravenous injection of neurotransmitters by the same workers (Fukada et al 1973) continued to suggest that the cricopharyngeus was under autonomic control, ie background cholinergic tonicity with superimposed alpha-adrenergic excitatory stimuli. Adrenergic nerves have not, however, been demonstrated in the UOS and there appears to be only somatic visceral efferent vagal innervation with additional supply from the glossopharyngeal and spinal accessory nerves, and no ganglia are present (Weisbrodt 1976).

Below the nodose ganglion, canine and human vagal anatomy differs in that the sympathetic supply is distributed with the vagus in the canine vagosympathetic trunks (Reid 1838). Above this level there also appear to be species differences. Hwang et al (1948) studied the motor innervation of the cervical oesophageal in six species of experimental animal, all of which exhibited double innervation by widely separated vagal branches. In the dog and cat, a separate pharyngo-oesophageal nerve was identified which shared a common origin with the superior pharyngeal nerve just above the nodose ganglion and was located posterior to the superior laryngeal nerve with whose external branch it communicated in half of the 48 dogs studied. It also had a fibrous (not nervous) connection to the superior cervical ganglion. Fine branches of the pharyngo-oesophageal nerve were noted to pass to the inferior constrictor of the pharynx, but its function was assessed only in the cervical oesophagus where it was found to provide the principal motor innervation. Stimulation of the recurrent laryngeal nerve was found to have no effect on the upper part of the cervical oesophagus and stimulation of the vagal trunks produced a contraction of the thoracic oesophagus. The importance of the separate canine pharyngo-oesophageal vagal branch in the control of the cricopharyngeus muscle was first studied by Lund and Ardran (1964) who used an 'isolated sphincter' preparation to show that no cricopharyngeal response was present in the dog when any part of the vagus nerve at or below the nodose ganglion was stimulated. Stimulation of the pharyngo-oesophageal branch of the vagus, however, produced a powerful UOS contraction. It was proposed that the nerve be called the nerve to the cricopharyngeus muscle because it appeared to provide the only efferent supply of the cricopharyngeus. Subsequent human dissections failed to reveal an equivalent separate vagal branch in man (Lund 1965a). This finding and the observation that no radiological abnormality of UOS function was present in a large number of patients with unilateral or bilateral recurrent laryngeal nerve palsy suggested that the human UOS and the pharynx were both supplied by the pharyngeal branch of the vagus. Lund (1965b) also demonstrated that while unilateral division of the nerve to cricopharyngeus produced no alteration in UOS function, bilateral division resulted in very weak relaxation and contraction of the sphincter. Freiman et al (1981) also showed no alteration in UOS tone following bilateral blockade of the vagosympathetic trunks below the nodose ganglion in a study of three dogs. More recently, however, Reynolds et al (1987) demonstrated a significant fall in UOS tonic pressure during a similar experiment in four cats. The change in UOS tone was attributed to blockade of recurrent laryngeal nerve impulses, implying some species differences in the importance of this nerve in UOS efferent supply. Human studies to date have failed to demonstrate UOS dysfunction following recurrent laryngeal palsy (Palmer 1976).

Weisbrodt (1976) states that intrinsic muscle activity is of little importance in striated muscle and reaffirms the contention (Doty 1968) that UOS closure is normally passive because of the structure and attachment of the cricopharyngeal musculature. In contrast, Hellemans et al (1970) demonstrated resting EMG striated muscle spike activity in the human UOS with deglutitive inhibition of electrical activity. In conclusion, it seems that the tonic contraction of the cricopharyngeus muscle is due to tonic vagal excitation. One or more motor units of the UOS region are in a constantly discharging state at rest (Christensen 1983).

1.3.2 Motor Innervation of the Oesophagus

Extrinsic nerves closely control the striated muscle of the cervical oesophagus which, like the pharynx, is innervated by somatic cholinergic vagal fibres (Doty 1968). These nicotinic nerve fibres can be blocked by curare or succinyl choline. There is also preganglionic parasympathetic vagal efferent supply. Post-ganglionic sympathetic fibres accompany blood vessels, although a few are distributed with the vagus in man (Goyal and Cobb 1981). Most are distributed to the myenteric plexus, with smaller components to the submucous plexus and directly to muscle fibres. The function of the sparse myenteric plexus, which extends to 1 cm below the cricopharyngeus, is not understood. As vagal efferents may end directly on muscle cells (Roman and Gonella 1987), the plexus may have a sensory function (Christensen 1983).

Peristalsis in the striated muscle oesophagus is thought to be due to successive motor unit discharge and no synapse or second-order neuron is involved. Hwang (1953) found cervical vagal blockade did not abolish cervical oesophageal peristalsis in dogs although recovery of peristalsis after pharyngo-oesophageal nerve section was thought to be due to recurrent laryngeal nerve activity. In the cat, however, peristaltic activity was abolished by bilateral vagal blockade below the nodose ganglion, suggesting an important efferent function of the feline recurrent laryngeal nerve (Reynolds et al 1987). In man, post-thyroidectomy dysphagia may be caused by damage to the oesophageal branches of the recurrent laryngeal nerve (Katz 1986).

Transection and suture of the striated muscle oesophagus in rhesus monkeys did not affect progression of the primary peristaltic wave, implying that the control of motor function in this area is largely central. In the smooth muscle oesophagus, however, transection and resuture abolished primary peristalsis, reflecting the greater importance of local control mechanisms in this area (Janssens et al 1976). This finding was anticipated by Kronecker and Meltzer (1883) who acknowledged that the central control mechanism could not be expected to overcome the effects of direct local stimuli. Similar results were obtained in human studies which showed that, while the proximal oesophagus was not significantly affected by swallow interval, at intervals of 8 sec or less there was a loss of contraction waves in the distal oesophagus. During continuous swallowing there was loss of contractions entirely below the UOS and only a single high amplitude peristaltic wave some seconds after the last swallow (Ask and Tibbling 1980). This phenomenon of deglutitive inhibition, originally described by Kronecker and Meltzer (1883), was later confirmed by Vanek and Diamant (1987).

The ganglion density of the smooth muscle oesophagus in some respects mirrors these clinical findings, as it shows a decrease from 1000 cells/cm^2 in the proximal parts to 100 cells/cm^2 in the region of the LOS, indicating a decreasing gradient in the density of innervation (Christensen 1983). The ganglia of the well-developed myenteric plexus of the smooth muscle oesophagus contain argyrophilic cells, while its intramural neurones are mostly argyrophobes. These neurones have branching axons to muscle and other effector cells where their terminals contain either small agranular (cholinergic), small granular (noradrenergic) or large opaque (non-cholinergic, non-adrenergic) vesicles. The latter contain a transmitter which may be purinergic or peptidergic (Goyal and Cobb 1981). In the opossum, this substance appears to open atypical potassium channels, which are resistant to several known channel-blocking agents (Jury et al 1985). In the rat oesophageal submucosa, the transmitter may be the peptide tachykinin substance P (Wiedermann et al 1987).

The only innervation which can be demonstrated in the longitudinal muscle of the oesophagus is excitatory and cholinergic, while the circular smooth muscle contains the non-cholinergic, non-adrenergic system which is both excitatory and inhibitory. Electrical stimulation of the distal stump of the severed vagus excites a progressive contraction. The importance of cholinergic pathways in this response was demonstrated by the inhibition by atropine of smooth muscle peristalsis in cats (Dodds et al 1978) and later in humans (Dodds et al 1981) in whom striated muscle peristalsis was unaffected. Additional findings indicated that basal LOS tone in humans and dogs, but not in opossums or monkeys, was in part due to cholinergic impulses.

The central nervous system controls primary peristalsis following volitional swallowing by vagal activation of sequential levels of the pharynx and oesophagus, but local reflexes are adequate to transmit secondary peristalsis, eg following balloon distension in an oesophagus totally separated from the central nervous system (Christensen and Lund 1969). Oesophageal smooth muscle does not possess phasic membrane potential oscillation ('pacemaker potential') at rest and it has been suggested that the progress of peristalsis is programmed within the myenteric plexus. This theory invokes two different neurotransmitters causing muscle inhibition and contraction (Diamant and El-Sharkawy 1977) but has since been contested, as the oesophagus has a relative paucity of ganglia compared with other gastrointestinal sites, and peristalsis is not slowed or abolished by ganglion blockade (Christensen 1983). According to Christensen, the organisation for the progression of muscle contraction is located within the circular muscle layer itself. The myenteric plexus is regarded as being almost simultaneously stimulated throughout its length while ionic intracellular gradients cause muscle contraction with a delay which increases progressively along the muscle segment.

Stimulation of the vagus nerves or of the oesophageal muscle by distension or by electrical square-wave impulses causes a transient onset contraction - 'on' response. The 'on' response is neurogenic (abolished by tetrodotoxin) and appears also to be suppressed by atropine and thus to arise from excitation of the vagal excitatory (cholinergic) pathway (Roman and Gonella 1987). After the 'on' response, the non-cholinergic non-adrenergic nerves to the circular muscle cause muscle inhibition during the period of stimulation (Christensen 1970). This inhibition is not normally detectable as the muscle is atonic at rest except in the LOS. After stimulation cessation, there is a vigorous contraction-'off' response (Christensen and Lund 1969). The progressive distal increase in latency of this 'off' response accounts for peristaltic wave progression. During inhibition there is hyperpolarisation and intracellular potassium accumulation. The almost simultaneous transmission of inhibition throughout the myenteric plexus also explains the early deglutitive relaxation of the LOS noted by Vantrappen and Hellemans (1967). This theory, then, invokes only a single non-cholinergic nonadrenergic oesophageal transmitter whose inhibitory hyperpolarisation is followed by a rebound depolarisation whose latency is due to a gradient in passive muscle potassium permeability (Christensen 1987). A recently-discovered 37-residue peptide, calcitonin gene-related peptide, has been demonstrated immunohistochemically in the myenteric neurones of the opossum oesophagus, where it appears to be an important inhibitory neurotransmitter (Rattan et al 1988).

Despite the complex local motor control mechanisms for autonomous peristalsis, the importance of cholinergic pathways (Dodds et al 1978 and 1981), the preservation of thoracic peristalsis following cervical deviation (Janssens et al 1976) and not least the presence of an extensive vagal supply whose single-pulse stimulation can cause excitatory and inhibitory effects (Roman and Gonella 1987) indicate that extrinsic innervation is likely to play a part in oesophageal body motility. Cholinergic nerves may mediate peristaltic velocity and cholinergic impulses passing to the longitudinal muscle cause shortening of the oesophagus which lasts throughout the stimulus train - the 'duration' response. Finally, the uniformity of peristaltic progression from striated to smooth muscle segments may be due to fine central control of the sequence, although the transition zone of mixed striated and smooth muscle fibres may be important in assuring the orderly progression of contraction (Christensen 1987).

In the opossum, vagal stimulation causes LOS relaxation and in the dog vagotomy abolishes LOS relaxation (Carveth et al 1962) while atropine causes a fall in human LOS resting pressure (Dodds et al 1981). The role of vagal fibres in LOS regulation remains to be clarified: there appear to be both inhibitory and excitatory vagal LOS fibres, and the picture is further complicated by the fact that atropine antagonises the motor effects of the sympathetic nervous system on the LOS (Roman and Gonella 1987). It has been proposed that in the opossum, LOS relaxation latency is mediated by 'M_1' muscarinic receptors which are antagonised by pirenzepine. The magnitude of LOS relaxation is determined by 'M_x' muscarinic receptors, ie those antagonised by atropine but not by selective blockade of M_1 or M_2 receptors (Gilbert and Dodds 1987). Early in vitro studies on opossum LOS relaxation also indicated that dopaminergic, beta-adrenergic and H_2-agonists were inhibitory transmitters (Christensen 1978). More recent experiments on isolated muscle strips from this species have shown that LOS relaxation induced by dopamine, isoproterenol or VIP is accompanied by an increase in intracellular cAMP, while electrical field stimulation produces LOS relaxation associated with an increase in cGMP (Torphy et al 1986). Calcitonin gene-related peptide also exerts a potent inhibitory effect on the opossum LOS, where it may act both by stimulation of non-cholinergic non-adrenergic inhibitory neurones and by a direct effect on sphincter smooth muscle (Rattan et al, 1988).

1.3.3 **Sensory Innervation of the Pharynx and Oesophagus**

Reid (1838) demonstrated that the glossopharyngeal was the principal sensory nerve of the pharynx and noted reflex movements in throat musculature following its stimulation in experimental dogs. Later studies of the initiation of swallowing in cats (Sinclair 1971) indicated that the glossopharyngeal was the primary afferent for pharyngeal stimulation of deglutition and bilateral glossopharyngeal section in the pigeon abolishes primary peristalsis in the distal cervical oesophagus (Postorino et al 1984). Swallowing can also be reflexly elicited by stimulation of the maxillary division of the trigeminal and the superior laryngeal nerve (Doty 1968) although only superior laryngeal stimulation is really effective in eliciting swallowing in all species tested (Miller 1982). In the cat, spontaneous afferent discharges from the superior laryngeal nerve are synchronised with respiration. Two types of superior laryngeal nerve discharge follow tactile stimulation: discharge from superficial receptors in the mucosa of the pharynx, supraglottis and trachea is abolished by topical anaesthesia; other discharges arise from internal laryngeal nerve endings. These are evoked by laryngeal compression and are not abolished by topical anaesthesia (Shin et al 1988). Both the superior laryngeal and glossopharyngeal nerves appeared to have larger central representations than the cephalic branch of the pharyngeal branch of the vagus in the cat and both are homogeneous mixed nerves in terms of fibre size. Later studies using horseradish peroxidase injection of the thoracic oesophagus revealed an unexpectedly distal distribution of canine glossopharyngeal afferents (Hudson and Cummings 1985). A gamma-efferent muscle-spindle arrangement is not present in the pharynx, except perhaps in the tensor palati (Goyal and Cobb 1981). The pharyngeal muscles may, however, contain a few proprioceptive nerve endings (Weisbrodt 1976). Within the mucosa, and in nerve plexi, free nerve endings abound. Sensory and autonomic substance P immunoreactive fibres have been demonstrated in the laryngeal mucosa of the dog, including the epiglottis, where their presence may be important in the prevention of aspiration (Shin et al 1987a and 1987b). The laryngeal surface of the epiglottis is more densely innervated than the pharyngeal surface in rabbits, cats, dogs and man but swallowing is most readily elicited from the pharyngeal surface or the edge of the epiglottis in man.

Freiman et al (1981) demonstrated that bilateral cervical blockade of the canine vagosympathetic trunks by cooling resulted in the abolition of UOS reflex responses to oesophageal acid infusion. It was concluded that the afferent limb of the response was carried exclusively in the vagosympathetic trunks, almost certainly in branches of the recurrent laryngeal nerves. The UOS response to oesophageal balloon distension was abolished only if the lumen were distended at least 10 cm below the UOS. In the proximal oesophagus it appeared that afferent impulses for distension were partly transmitted by a pathway entering the vagus above the level of cervical cooling. A subsequent series of similar experiments in cats demonstrated complete abolition of UOS responses to acid infusion or distension of the proximal 5 cm of the oesophagus (Reynolds et al 1987). The authors concluded that either all the afferent fibres from the proximal oesophagus travelled in the cervical vagal trunks or that the efferent limb of the UOS reflex responses had been abolished by cervical cooling blockage but with preservation of higher afferent pathways. In Reynolds' study, however, the animals were investigated under light anaesthesia while those in Freiman's tudy were awake and this may have contributed to the different findings in the two studies, which were also performed in different species.

From the midoesophagus afferent fibres pass to the recurrent laryngeal nerve and from the lower oesophagus to oesophageal branches of the vagus. Many researchers have attempted to establish the importance of oesophageal afferent innervation in the generation of oesophageal peristaltic waves. Meltzer (1899) reached the conclusion that previous reports of the abolition of peristalsis after oesophageal wall section were erroneous and due to the deep level of general anaesthesia employed. He also considered that peristaltic contractions could not be caused by direct stimulation of oesophageal musculature alone as peristalsis was abolished in animals following vagal section. Local generation of a peristaltic wave after the introduction of liquid directly into the rabbit oesophagus was also abolished by vagal section, and thus thought to be reflex, not mechanical (Meltzer 1906). Such local oesophageal reflex mechanisms were thought to provide a supportive function to the primary central generation of the peristaltic wave. Later experiments in dogs suggested, however, that swallowing in the absence of a bolus did not produce peristalsis, although the threshold for the production of a peristaltic wave was reduced if a deglutition were allowed at the time of bolus entry (Jordan and Longhi 1971). Nonidez (1946) demonstrated afferent nerve endings around canine myenteric plexus ganglia and proposed that their function was to control eating, and to prevent excessive stretch of the oesophageal wall. Stimulation of these mechanoreceptors also produces relaxation and shortening of the LOS in response to balloon distension (Price et al 1979). The dog has no intramural pathway for such reflexes, unlike other species with smooth muscle oesophagi, and the LOS responses were blocked by vagosympathetic blockade, in keeping with Meltzer's original observations.

It is now accepted that for oesophageal peristalsis elicited by swallowing (primary peristalsis), the principal control mechanism is central, but also that afferent input from the oesophagus influences both the intensity and timing of central discharges and the peripheral control mechanisms of peristalsis (Diamant and El-Sharkawy 1977). Hence the findings that although primary peristalsis is preserved after bolus deviation in the rhesus monkey in either the cervical or smooth muscle oesophagus, the presence of a bolus facilitates progression of primary peristaltic waves, and also that smooth muscle peristalsis follows superior laryngeal nerve stimulation even after the striated segment is paralysed by curare (Janssens et al 1976). Secondary peristalsis, in response to the presence of a bolus, is confined to smooth muscle fibres even in the transition zone, and the fact that it can originate in such fibres even above a transected area confirms Meltzer's suggestion that it is vagally mediated. In man, peristatic waves have been shown to follow either swallowing or the admission of a large incompressible bolus into the oesophagus (Vantrappen et al 1967) and it is reasonable to conclude that oesophageal mechanoreceptors are the source of afferent input for the generation of secondary peristalsis, and for the facilitation of primary peristalsis in the presence of a bolus. Oesophageal mechanoreceptors also provide reflex control of UOS function in response to oesophageal balloon distension in man (Creamer and Schlegel 1957, Enzmann et al 1977, Gray et al 1979, Andreollo et al 1988) and indirect evidence suggests that oesophageal osmoreceptors may influence upper and lower oesophageal motility (Siegel and Hendrix 1963, Wallin et al 1978, Gerhardt et al 1978). Pain receptors are also present with the oesophagus and it is possible that their sensitivity reflects a general alteration in afferent discharge in individuals affected by oesophageal chest pain (Richter et al 1986a). These receptors are also involved, of course, in the generation of heartburn, which is much the commonest oesophageal symptom, affecting at least one third of the general population (Thompson and Heaton 1982).

Although stimulation of pharyngeal receptors is the normal trigger for a deglutition response, any further role of sensory input at this level remains controversial. Magendie (1823) observed that repeated dry swallows (of saliva) became increasingly difficult, a finding which is readily confirmed and Lund (1965b) showed that cricoid movement increased with increasing bolus volume. Sandberg and Mansson (1984) found that the time taken to perform 10 such dry swallows was reduced by salivary secretogogues and increased not only by atropine but also by topical anaesthesia of the pharynx. The same authors had previously demonstrated that extensive oropharyngeal anaesthesia produced coughing and incoordination of swallowing, with a reduction in UOS relaxation time (Mansson and Sandberg 1974). Their conclusion was that sensory information was necessary for normal swallowing.

Conley (1960) also reported that bilateral surgical division of the superior laryngeal nerves resulted in clinical dysphagia, a symptom well-known to relate to bolus qualities which affect the magnitude of laryngeal aspiration (Linden and Siebens 1983). At a central level, Sumi (1964) reported no significant change in the swallowing pattern of discharge in the hypoglossal and ambiguus nuclei when all sensory feedback was prevented by motor paralysis. Such paralysis abolished all response in the neurones of the tractus solitarius and it was concluded that this nucleus represented a simple relay for oropharyngeal afferents rather than a true swallow centre, although the general anaesthesia employed might have affected results (Mansson and Sandberg 1974). Others also reported the pharyngeal stage of swallowing to be unaffected by cocainisation of the pharynx (Doty and Bosma 1956, Bosma 1957). The most recent work in this area, using manofluorography in unanaesthetised humans (Cook et al 1988a and b) suggests that the area and duration of UOS relaxation, among other parameters, are dependent on the size of the bolus swallowed under physiological circumstances. The authors conclude that, as anticipated by Magendie over 150 years ago, sensory feedback does indeed modify the swallowing pattern generated by the brain stem.

1.3.4 Central Integration of Swallowing

The concepts of the central integration of deglutition with other visceral functions stem from the early work of Kronecker and Meltzer (1881). The central swallowing mechanism has 3 components - the afferent and efferent systems with an interposed internuncial regulatory network. The motor neurones of swallowing are the trigeminal, facial hypoglossal and the nucleus ambiguus whose efferents are distributed via the glossopharyngeal, vagal and spinal accessory nerves to innervate the larynx, pharynx and striated cervical oesophagus. The smooth muscle of the oesophagus is supplied by the dorsal nucleus of the vagus. The nucleus ambiguus extends from a position caudal to the facial nucleus in the pons to the level of the spinomedullary junction and supplies special visceral efferents (Hudson and Cummings 1985). The vagal nucleus lies in the vagal trigone in the floor of the fourth ventricle and the term 'dorsal nucleus' is used to distinguish the general visceral efferent cell bodies for oesophageal smooth muscle from the sensory, cardiac and secretomotor salivary cell bodies (Last 1978). The precise anatomical level where nucleus ambiguus supply is taken over by dorsal nucleus efferents is not known. Although cricopharyngeal myotomy was introduced for the surgical relief of dysphagia following poliomyelitis (Kaplan 1957), the relative sparing of the cricopharyngeus in bulbar poliomyelitis led Kramer et al (1957) to suggest that the dorsal nucleus efferents might begin at the level of the lower pharynx (as the dorsal nucleus is much less affected than the nucleus ambiguus in this condition) and to question the rationale of cricopharyngeal myotomy.

The converse proposition, ie that the nucleus ambiguus special visceral efferents extend further distally than has previously been thought, was suggested by Hudson and Cummings (1985) following a series of experiments of whole wall dog oesophagus injections with horseradish peroxidase. At all levels, central neurones could be identified in both the nucleus ambiguus and the dorsal nucleus. In neither nucleus was there evidence of somatotopic organisation of neurones, in contrast to the known somatotopic organisation of nucleus ambiguus cells supplying laryngeal musculature in the cat, rabbit or monkey.

A report by Doty et al (1967) indicated that lesions of the reticular substance between the posterior pole of the facial nucleus and the rostral pole of the inferior olive suppressed the swallow response provoked by superior laryngeal nerve stimulation. Each lateral half swallow-centre was thought to excite constrictor muscles contralaterally and other muscles ipsilaterally ('crossed constrictor response'). It has since been established, however, that afferent impulses pass to the fasciculus solitarius whose fibres synapse with the second order neurones of the nucleus tractus solitarius which is located lateral to the superior salivatory nucleus 2 - 4 mm in front of the obex (Last 1978, Roman and Gonella 1987). Impulses also pass to the descending trigeminal tract whose fibres also enter the nucleus tractus solitarius. Remaining afferents pass to the commissural nucleus of Cajal (Christensen 1987). Stimulation of either the solitary tract or nucleus will elicit deglutition (Hockman et al 1979) but stimulation of frontal cortical areas which project to the medullary swallowing centre will also produce a swallow response (Doty 1968). Subcortical areas which facilitate deglutition include the internal capsule, hypothalamus, substantia nigra and amygdala (Hockman et al 1979) and the raphe obscurus (Holtman et al 1987). The raphe obscurus appears to influence recurrent laryngeal nerve neurones in the nucleus ambiguus, a pathway which is, in part, serotonin mediated. The presence of these supramedullary areas which facilitate deglutition may explain the transient dysphagia following cerebrovascular accidents and head injuries, irrespective of the site of the lesion (Winstein 1983, Gordon et al 1987). Laryngeal dysfunction is found only after brain stem lesions (Veis and Logemann 1985). On the other hand, the human foetus begins swallowing at 12 weeks in utero, well before the cortical and subcortical areas have developed (Miller 1982). There is also evidence for pontine centres of deglutition in sheep and rabbits: the dorsal site communicates with the thalamus and with caudal pathways, while the ventral site can facilitate medullary pathways of deglutition (Miller 1982).

Doty and Bosma (1956) proposed that the deglutition reflex was independent of both afferent impulses and of collateral linkages between motor nuclei but more recent studies have characterised the function of nucleus tractus solitarius and associated neurones in greater detail. There are three groups of neurones which discharge early (buccopharyngeal), late (upper oesophageal) or very late (distal oesophageal). The discharge of these neurones is now known not to represent a simple feedback in response to muscular activity as it is present even after curarisation and, in some neurones, begins before the onset of swallowing. Also, partial destruction of the nucleus solitarius can abolish deglutitions elicited by superior laryngeal stimulation (Kessler and Jean 1985). Early neurones are located in and around the hypoglossal and rostral ambiguus nuclei and the solitary tract (Hockman et al 1979). Late neurones are around the solitary tract and the dorsal nucleus of vagus. The latter may also receive vestibular nucleus projections relevant to alterations in gastro-oesophageal motility following caloric and other stimuli which induce nausea in association with vertigo (Caria et al 1988).

A more recent study in the rat (Kessler and Jean 1985) identified two major neuronal populations - Group I neurones with a short (1 - 4 msec) latency response to superior laryngeal nerve stimulation, thought to be programming interneurones and Group II neurones, some of which also exhibited an initial response to superior laryngeal nerve stimulation (but with an increased latency of 7 - 12 msec). The Group II neurones are thought to be motorneurones and interneurones forming the efferent stage of the swallowing centre. Neurones in the nucleus tractus solitarius and adjacent reticular substance have either a phasic discharge on swallowing or exhibit a spontaneous activity which is enhanced or inhibited by deglutition. The process of central programming may be linked to successive inhibition of interneurones, with a series of postinhibitory rebounds (Roman and Gonella 1987). The early conclusions of Meltzer's experiments, for example, that the pharyngo-oesophageal nerve was a specific inhibitory pathway for deglutition would probably be more rightly attributed to the inhibition of late/very late neurones during the discharge of early neurones.

The mature human swallows on average 600 times per day (Lear et al 1965). The performance of so complex a reflex thus frequently clearly implies integration of the swallowing reflex with other visceral functions (Kawasaki et al 1964b). Sucking, breathing and swallowing in infants take place in a relatively fixed ratio of 1:1:1 (Doty 1968). Swallowing is also integrated with respiration in the adult human. Superior laryngeal nerve stimulation inhibits phrenic nerve discharge and the superior laryngeal nerve threshold for respiratory inhibition is less than that for swallowing. Clark (1920) noted that the majority of swallows occur during expiration, with a respiratory pause of less than 2.5 sec. Doty and Bosma (1956) also noted that the majority of swallows in deeply anaesthetised dogs, cats or monkeys occur during expiration, but that under lighter anaesthesia 80% of swallows in the dog and monkey occurred during peak inspiration. In the fully conscious dog, 94% of swallows occur during the inspiratory phase (Kawasaki et al 1964a). The brief inspiration ('swallow-breath' or 'Schluckatmung') which may accompany swallowing is variably observed (Doty and Bosma 1956, Donner 1985).

Studies comparing the subglottic pressure in cats and humans with afferent discharge in the superior and recurrent laryngeal nerves indicate that although activation of the respiratory muscles occurs during swallowing, there is no inspiration or expiration of air as the glottis remains closed (Shin et al 1988). Meltzer (1883) thought that the respiratory changes associated with swallowing were due to the mechanical interruption of air flow by the apposition of the base of the tongue to the epiglottis but it is now known that the deglutition response of the medullary respiratory neurones precedes even that of the nucleus tractus solitarius (Sumi 1964). Chemical stimulation of the carotid body chemo-receptor afferents also evokes potentials in the nucleus tractus solitarius and adjacent reticular substance, whose neurones respond with the generation of spontaneous respiratory rhythms. Most of the respiratory neurones are in the ventrolateral nucleus, driven by vagal input from the pulmonary stretch receptors of the Hering-Breuer reflex, with most of the active projections being to phrenic nerve neurones (Miller 1982). There are also cardiovascular inputs to the solitary nucleus, both baro- and chemo-receptor afferents, which project to the dorso-medial areas. The central swallowing areas may also modify the pattern of pharyngo-oesophageal motility during sleep: during sleep, when UOS resting tone is reduced, not all swallows are associated with UOS relaxation, although a pharyngo-oesophageal peristaltic wave is present (Kahrilas et al 1987b). The swallow frequency is also reduced druing speep from a mean of 1.6/min to 0.24/min during stage I sleep. During deep sleep, there are fewer than four swallows per hour, although other factors, such as the rate of salivary flow are probably of equal importance to the central regulatory mechanisms in determining sleep swallow freqeuncy.

2. PHARYNGO-OESOPHAGEAL MOTILITY

2.1 EARLY THEORIES OF THE DEGLUTITION MECHANISM

'Though deglutition is very simple in appearance it is nevertheless the most complicated of all the muscle actions that serve for digestion' - Magendie 1823.

The essential features of the deglutition mechanism were described in the 17th century by William Harvey, who remarked upon their speed and coordination, and noted the propulsive role of the tongue base, the closure of the larynx by its intrinsic musculature and the elevation and dilatation of the pharyngo-oesophageal junction. In his detailed description of 1823, Magendie divided swallowing into three phases - oropharyngeal, pharyngo-oesophageal and oesophagogastric. Magendie's oropharyngeal stage comprised anteroposterior compression of the bolus by the tongue on the palate. During the second phase, the great rapidity of bolus passage past the glottic opening was noted to be enhanced by the elevation of the hyoid apparatus, upward cricoid tilt and pharyngeal propulsion. Magendie considered the principal laryngeal sphincter mechanism to be closure of the true cords and that all the phenomena of the second stage were not only involuntary but simultaneous. Despite the observed inaccessibility of the oesophagus, he also noted differences in circular muscular function between its upper and lower parts, in particular the relative delay in lower oesophageal peristaltic contraction compared with bolus passage which he believed might take up to three minutes. While this estimation of bolus transit was clearly erroneous, the occurrence of peristaltic contraction after the bolus had reached the stomach was confirmed by dog and human experiments later in the 19th century (Kronecker and Meltzer 1881). Liquid bolus passage was then believed to be accomplished in less than 0.1 sec, while peristalsis took 6 sec to reach the gastro-oesophageal junction. Upper oesophageal contraction was thought to last 2 - 3 sec and distal contraction

8 - 9 sec, with peristaltic latency showing similar abrupt increases at increasingly distal sites. The rapid passage of the bolus was believed to be due to a squirting motion of the mylohyoid and lingual muscles as swallowing was not affected by removal of the cervical oesophageal musculature or even, in one dog, by the removal of the middle and inferior constrictors (Meltzer 1907). Swallowing was also recognised to be an all-or-nothing phenomenon - 'alle Glieder oder keines' (Meltzer 1883).

Killian (1908) believed the most sensitive site for eliciting a swallow reflex was the posterior wall of the pharynx, but that deglutition was primarily a voluntary phenomenon as it could occur in the absence of such stimulation and also because of voluntary imbibition of large volumes by beer-drinkers with an open 'oesophageal mouth' but without hyoid elevation or swallowing movements. Killian's three phases of swallowing comprised: (1) the 'Einstellungsphase', comparable to Magendie's oropharyngeal phase but including also a 'Schluckatembewegung' or swallow breath movement of the diaphragm, (2) 'Austreibungsphase' including forward movement of the hyoid, and expulsion of the bolus towards the stomach and (3) 'regressive Phase' during which the intrapharyngeal pressure fell and the larynx descended. Each phase was thought to last 0.25 sec, in contrast to the longer oesophageal phase which lasted 1.5 sec in the cervical portion and 4.5 sec in the thoracic segment and was thought merely to convey any upper residuum of food towards the stomach. The duration of UOS relaxation was thought to be 0.24 - 0.48 sec.

Negus (1925) believed that the principal role of the circular muscle was to restrain the bolus while the longitudinal fibres drew the gullet up over it, and described the resting relaxation of the pharyngeal musculature, in contrast to the resting tonic pressure of the cricopharyngeal sphincter, achalasia of which was believed to be important in the aetiology of pharyngeal pouch. The later suggestion and apparent manometric confirmation of a negative pressure wave causing the bolus to be 'sucked in' to the oesophagus (Barclay 1934) was disputed by Negus (1949, 1950) on the basis of clinical observations confirming a 'pharyngeal force pump' in patients with pharyngostomes and by Saunders et al (1951) who failed to demonstrate a 'suction' mechanism radiologically. The protective role of the epiglottis during swallowing was reviewed by Bosma (1957) who concluded that its base provided additional protection for a general closure of the laryngeal vestibule during laryngohyoid convergence of the second stage which also brought the cricopharyngeal sphincter up to the level of the closed vestibule. Lack of laryngohyoid movement produced marked dysphagia which could be overcome by a variety of mechanisms, including positional adaptation and muscle transplantation. It has long been observed that normal swallowing occurs with the mouth closed (Passavant 1869) and it is likely that the difficulty in swallowing with the mouth open is due to impediment of laryngohyoid movement.

The limitations of investigative methodology at this time led to continued debate about cricopharyngeal function. Although Templeton and Kredel (1943) were able to demonstrate radiologically a cricopharyngeal impression which was displaced anteriorly during inspiration, they concluded the cricopharyngeus responded passively to pharyngeal pressure changes. The first definitive work on pharyngo-oesophageal pressure dynamics came from Fyke and Code (1955) who demonstrated a 3 cm long manometric high pressure zone whose upper margin was a mean of 16.5 cm from the incisor teeth and which lay opposite the cricoid cartilage, corresponding, therefore, to the cricopharyngeus. Increases in UOS pressure were observed both before and after deglutitive relaxation which preceded bolus passage, and a small positive pharyngeal deflection was observed before the major propagated pharyngeal wave. The maximum UOS relaxation pressure was 40 cm of water below resting oesophageal pressure, and the 'instantaneous character' of this negative deflection was taken to imply an association with the initial movements of swallowing. The electromyographic studies of Doty and Bosma (1956) also demonstrated that inhibition of cricopharyngeal muscular activity was an essential component of swallowing and supported the concept of consecutive activation of the mouth, pharynx and oesophagus.

The following year, Atkinson et al (1957) published their findings with manometric recordings from three levels in the pharyngo-oesophageal segment, with simultaneous radiographic analysis. The UOS length was recorded as 1 - 4 cm, with a mean pressure of 35 mmHg. Intrasubject variability was interpreted as a genuine variability in UOS pressure. The deglutition pattern was described as an abrupt fall in UOS pressure to the level of, but not lower than intraoesophageal pressure, followed by return to resting pressure which was sometimes altered. This alteration was explained either as a real change in tonic pressure or as a movement artifact due to movement of the tube into the oesophagus with the bolus. Where observed, a UOS after-contraction was thought, on radiological grounds, to be due to the latter. Pharyngeal contractions were double-peaked. The first may have been due to bolus passage; the second was larger and corresponding to constrictor contraction. The two waves almost merged into a single peak in the upper pharynx. An increase in amplitude and duration of pressure complexes during bread swallows, and the ability of one subject to admit considerable volumes of water into the oesophagus without swallows, was also described. Like Fyke and Code, the authors also noted an initial negative oesophageal wave, attributed to oesophageal stretch during laryngeal elevation, or to an inspiration ('swallow breath'). Bolus speed was 40 - 50 cm/sec in the pharynx, compared with a peristaltic wave velocity of 5 - 10 cm/sec. There was no evidence of a marked negative pressure in the pharyngo-oesophageal segment as suggested by the radiological studies of Barclay (1934) or the manometric studies of Fyke and Code (1955).

A further early manofluorometric study (Sokol et al 1966) showed results similar to those of Atkinson et al (1957). Resting UOS pressure was found to be greater than 45 mmHg, and UOS length ranged from 2.5 to 4.5 cm with a 1 cm zone of maximum pressure. A triple-peaked pharyngeal wave was, however, recorded from the mid-pharynx. Small early 'e' and 't' waves were attributed to elevation of the larynx and movement of the tongue respectively. These preceded the peristaltic 'p' wave, which followed the passage of barium. The 'e' wave was minimal or absent in the cricopharyngeus. The 't' wave was thought to account for a brief pressure rise between maximum relaxation and the plateau of (less-marked) relaxation which preceded UOS after-contraction. The descending limb of this contraction or 'p' wave was observed to diminish towards maximal UOS resting pressure, to a point where resting pressure was sometimes as great as maximum after-contraction and there was no descending limb. The 't', but not the 'e', wave was also seen to precede contraction in the upper oesophagus. Duration of relaxation (0.25 - 0.4 sec) was similar to that observed by Atkinson et al (1957). UOS after-contraction had an amplitude of 50 - 75 mmHg and a duration of approximately 2 seconds.

Later EMG and manometric studies in dogs (Kawasaki et al 1964a and b) showed a brief negative intratracheal pressure which returned to zero by the time of peak pharyngeal contraction which was achieved within 0.075 sec. There was a delay of 0.1 sec between mylohyoid contraction and the onset of thyroarytenoid activity which was followed 0.35 sec later by the onset of cricopharyngeal contraction. The cricopharyngeal relaxation interval of 0.4 sec was similar to those of Killian (1908) and Lund (1965b). Shin et al (1988) showed that the drop in intratracheal pressure was a temporary fall coinciding with laryngeal elevation and was preceded and followed by periods of increased subglottic pressure, corresponding to the onset of deglutition and to the descent of the larynx. This pattern was unaffected by unilateral recurrent laryngeal nerve section.

Like Fyke and Code (1955), Lund (1965b) also observed a small pre-relaxation UOS contraction during dog experiments which he attributed to mechanical displacement of the sphincter upwards by the pull of the transducer. He considered, however, that the post relaxation UOS after-contraction represented true muscular activity and not a movement artifact as suggested by Atkinson et al (1957), and by use of the 'isolated sphincter' preparation confirmed the observations of Doty and Bosma (1956) that relaxation was also a muscular phenomenon and did not merely represent UOS opening by forward pull of the cricoid or cartilages of Santorini. In contrast, the later EMG studies of Shipp et al (1970) suggested that the principal cricopharyngeal event was a simple loss of baseline electrical activity during contraction of the upper part of the inferior constrictor.

Important additional conclusions from Lund's cineradiographic studies in man were: (1) that the UOS did not open ahead of the bolus; where this appeared to occur there was, in fact, air ahead of the solid bolus and (2) that larger boluses excited a greater degree of cricoid movement and of UOS opening, in contrast to the assertion by Bosma (1957) that swallowing was independent of bolus properties. Lund also proposed a mechanism of propagation in the pharynx similar to that later proposed by Christensen and Lund (1969) for the smooth muscle oesophagus, ie an initial relaxation wave, most evident in the cricopharyngeus, followed by a propagated contraction wave.

Although Sokol et al (1966) felt the 'e' component of the pharyngeal wave was certainly due to laryngeal elevation, the origin of the 't' wave below the oropharynx was uncertain and the effects of respiratory and deglutitive movements on observed motility patterns in the pharyngo-oesophageal segment remained unclear. Vantrappen and Hellemans (1967) concluded that small initial negative deflections observed before one third of peristaltic waves in the normal human oesophageal body were due to an inspiratory fall in intrapleural pressure during swallowing. Goyal et al (1970) observed an increase in tonic UOS pressure on inspiration during a manometric study of 25 normal subjects. The brief prerelaxation increase in UOS pressure was only variably observed, although thought to represent a protective mechanism against oesophageal air entry rather than a movement effect as had been thought previously.

2.2 CURRENT CONCEPTS OF PHARYNGO-OESOPHAGEAL MOTILITY

'The whole question of function and control of the upper esophageal sphincter merits much more investigation than it has previously received. In a sense, the sphincter represents the first obstacle to be overcome by the ingested food and the last barrier which prevents spilling of reflux material from the esophagus into the pharynx' - Pope et al 1975.

The first of the three stages of swallowing observed by Magendie (1823) and Killian (1908) was later divided into four phases on the basis of cinefluorographic studies (Miller 1982): (1) the collection of food in a central lingual hollow, (2) the anterior alveolar phase during which the tongue tip is placed against the anterior alveolar ridge and the incisors approximate, (3) the midpalatal phase as the bolus is squeezed back between the tongue and palate and (4) the compression phase, immediately preceded by moderate hyoid elevation during which the bolus moves between the tongue, the approximated soft palate, the constrictor wall and the epiglottis. During the oral phase, increased bolus consistency increases propulsive pressure (Shaker et al 1988a). Partial leakage of the bolus during this latter phase into the superior laryngeal nerve territory may be the initiator of the pharyngeal reflex. The pharyngeal component has two main elements: an upward movement and a downward peristaltic wave, whose resultant 'engulfing' takes approximately 0.1 sec in mature humans, with an ejection velocity up to 100 cm/sec.

A major breakthrough in understanding of cricopharyngeal function followed the description by Winans (1972) of UOS radial asymmetry. Mean UOS pressure in the anteroposterior plane was three times greater than that recorded from laterally orientated ports. This asymmetry was thought to represent the pattern of activity of the cricopharyngeus and was later confirmed by Berlin et al (1977) who also demonstrated a fall in UOS pressure following cricopharyngeal myotomy. In the same year, Enzmann et al

(1977) demonstrated an augmentation of UOS pressure in response to balloon distension by at least 20 mmHg from a resting pressure of 35 to 90 mmHg. The UOS response to balloon distension was confirmed recently by Andreollo et al (1988) who showed an increase of 95 mmHg in UOS pressure at maximum tolerated distension. This response, like inspiratory augmentation (Goyal et al 1970) and axial lengthening (Winship 1983) might also serve a protective purpose as UOS hypotonicity and diminished response to experimental introduction of intraoesophageal fluid 10 cm below the UOS have been reported in patients with oesophagopharyngeal regurgitation (Gerhardt et al 1980a). Clinically GOR could not, however, be demonstrated to cause an elevation of UOS pressure (Berte and Winans 1977). This may be because the consequent oesophageal dilatation is too slight, or too distal as UOS responses are related to both degree and proximity of experimental distension (Gray et al 1979). Conversely, the UOS relaxes during belching and in response to oesophageal distension by air (but not fluid). If balloon distension is sufficiently rapid and over a long segment, it too can induce UOS relaxation as opposed to augmentation (Kahrilas et al 1986).

Despite the demonstration of UOS radial asymmetry, reports of length and pressures continued to be wide-ranging (Roed-Petersen 1979a). Some workers who included minor pressure elevations at the upper and lower limits of the sphincter recorded lengths in the region of 5 cm (Goyal et al 1970). The variability was probably also a reflection of axial UOS asymmetry and perhaps of artifacts caused by catheter movement (Levitt et al 1965). Gerhardt et al (1980b) noted peak posterior UOS pressures were 0.55 cm more distal than peak anterior pressures and observed axial lengthening of the high pressure zone on fluid infusion into the oesophagus. Axial asymmetry had previously been noted in the opossum (Asoh and Goyal 1978) and in a study of the effect of laryngectomy on the UOS (Welch et al 1979) which, unlike the report of Gerhardt et al (1980b), failed to show significantly lower pressures in the anterior than in the posterior plane. It was not clear whether the axial UOS asymmetry was caused by the angle of attachment of the cricopharyngeus or by the contribution of other muscles to the high pressure zone. It can, however, be concluded from these findings that the debate about whether it is upper oesophageal or lower inferior constrictor fibres which act with the cricopharyngeus to form the upper high pressure zone was over-simplified. Loss of radial asymmetry following laryngectomy suggests that the cartilaginous framework of the larynx may be responsible for at least part of the asymmetry (Welch et al 1979).

The wide range of reported tonic UOS pressures is due not only to the physiological variables discussed above, but also to methodological difficulties (discussed in Section 2.3). Many authors report mean tonic UOS pressures in normal subjects to be less than 50 mmHg (Fyke and Code 1955, Atkinson et al 1957, Sokol et al 1966, Pedersen et al 1973, Stanciu and Bennett 1974, Dodds et al 1975, Hurwitz et al 1975, Roed-Petersen 1979b, Duranceau et al 1983a). Watson and Sullivan (1974) and Weihrauch (1980b) record tonic pressures in excess of 100 mmHg. Others, like Winans (1972) and Berlin et al (1977) report different lateral and anteroposterior pressures (Gerhardt et al 1978, Welch et al 1979, Hellemans et al 1981). Anteroposterior pressures are in the region of 80 - 120 mmHg, while lateral pressures are usually less than half of these values. Peak UOS after-contraction pressures are in the region of 90 mmHg (Dodds et al 1975, Duranceau et al 1983a) or greater (Pelemans 1983). The highest tonic pressures reported are so great as to be liable to compromise vascular perfusion, leading Christensen (1987) to postulate that the presence of the catheter may reflexly increase contraction force.

The duration of UOS relaxation, originally estimated at 0.4 sec (Killian 1908, Kawasaki et al 1964a, Lund 1965b) was later calculated as 0.8 to 1 sec (Dodds et al 1975, Roed-Petersen 1979, Fulbeck et al 1980, Hellemans et al 1981) although the duration may be overestimated if the recording system has a slow rate of rise in reponse to UOS after-contraction (Hellemans et al 1981). Interestingly, a recent study (Kahrilas et al 1988a) has shown the duration of the maximum UOS relaxation to be 0.37 sec, ie close to historical estimates, during dry swallows, increasing to 0.65 sec for 20 ml wet swallows. Reports of pharyngeal contraction amplitude vary widely from 34 mmHg (Duranceau et al 1983a) to greater than 600 mmHg in some individuals (Dodds et al 1975); duration of pharyngeal peristalsis is more consistently reported at around 0.4 sec. This figure may be greater in the upper pharynx where the tongue or 't' wave of the oropharynx may blend with the peristaltic wave (Goyal and Cobb 1981). The pharyngeal wave travels at approximately 15 cm/sec to reach the UOS in 0.67 sec.

The criteria for assessing coordination of pharyngeal contraction and UOS relaxation depend on the investigative method used to assess motility. Pure manometric criteria for adequate coordination which do not, of course, take account of the passage of the swallowed bolus, have been listed as a relaxation of the UOS to within 5 mmHg of cervical oesophageal baseline, entirely encompassing pharyngeal contraction and a peak pharyngeal pressure coincident with the nadir of UOS relaxation. Such criteria are said to be fulfilled in over 90% of normal swallows (Duranceau et al 1983a). This concept of normal coordination does, however, depend on the characteristics of the recording system used. A slow frequency-response might delay the registration of UOS after-contraction which may, in fact, begin before pharyngeal contraction is complete in normal subjects. The relative timing of pharyngeal and UOS pressure events clearly depends on the level at which pharyngeal recordings are made and, as far as bolus transit is concerned, the velocity of pharyngo-oesophageal ejection increases with the size of bolus swallowed (Fisher et al 1978, Cook et al 1988a) and is also dependent on gravity. Increases in bolus volume also cause increases in UOS crosssectional area and duration of relaxation and progressively earlier onset of laryngohyoid movement and UOS relaxation (Kahrilas et al 1988a, Cook et al 1988a and b). In other words,both recording and bolus variables require to be standardised before precise criteria for manometric normality in the pharyngooesophageal segment can be established. Other factors to be considered include the test conditions, as it has been shown that stress can induce increases in tonic UOS pressure (Cook et al 1987).

2.3 REVIEW OF INVESTIGATIVE TECHNIQUES

'If to the infrequency of the diseases of the oesophagus we add the trivial character of the symptoms by which many of the more frequent but slight affections are accompanied and the fact that, during life, the organ is entirely out of sight, we can understand the very slight interest which has been shown by physicians in disturbances of this region' - Zenker and von Ziemssen 1878.

As technology and investigative skills developed from the 1940s onwards, so there was a great increase of interest in the physiology and pathology of motility disorders of the oesophagus. The pharyngo-oesophageal segment has been the last area to be subjected to careful manometric study because of the associated methodological problems, some of which have already been alluded to - the rapid sequence of events on deglutition, radial and axial asymmetry of the UOS and sensitivity of the area to water from perfused catheter systems and perhaps to the presence of the catheter itself. Early studies relied on radiological investigations which have, in recent years, been combined with manometric methods in manofluorometry. Electromyographic studies have also been carried out although their results usually yield more rapid patterns of pharyngo-oesophageal dynamics than either radiology or manometry. Radiology has the obvious disadvantage of exposure of subjects (particularly if healthy volunteers) to radiation, but gives useful information about bolus passage not obtainable by manometric methods, which are only now becoming sufficiently reliable to be useful. In addition, because there has long been an awareness among clinicians that upper oesophageal events may be influenced by lower oesophageal motility, in particular GOR, techniques such as prolonged ambulatory pH monitoring have been used to supplement investigations of pharyngo-oesophageal motility. Psychometric assessment also has a part to play in clinical investigation as there have now been several studies indicating links between psychological parameters and oesophageal motility.

2.3.1 Radiological Investigation and Manofluorometry

Before the discovery of X-rays by Roentgen in 1896, oesophageal investigation was confined to the passage of sounds (Munro 1811) and the early attempts at endoscopy by Kussmaul and Mikulicz. The bismuth swallow was introduced by Cannon and Moser (1898) who concluded that liquids were ingested by the squirt mechanism proposed by Kronecker and Meltzer (1883) but that solids and semisolids were propelled by oesophageal peristalsis. The only human studies were, however, performed in a seven year old girl. Subsequent radiological investigation in the early 20th century led to the suction theory of deglutition (Barclay 1934) and to the definition of a wide variety of causes of dysphagia (Otell and Coe 1935). In early 'spot' film or fluoroscopic studies, the posterior pharyngeal indentation was identified as the cricopharyngeus (Jonsson 1937, Templeton and Kredel 1943) although it required to be distinguished from cervical exostosis (Mosher 1926). In a study of 50 asymptomatic patients, 29 were found to have a slight cricopharyngeal impression and seven a more prominent bulge (Siebert et al 1959) but Seaman (1966) identified a cricopharyngeal impression in only 5% of subjects and considered the finding a sign of neuromuscular dysfunction and Schobinger (1958) found that increased cricopharyngeal prominence after laryngectomy was associated with dysphagia.

The advent of high-speed cineradiography allowed more detailed study of pharyngo-oesophageal dynamics. Saunders et al (1951) found the optimum film speed to be 30 - 60 frames/sec, which allowed observation of tongue, palatal and pharyngeal movements. Rushmer and Hendron (1951) used pharyngeal strain gauges in conjunction with cineradiography and found pharyngeal pressures of 40 - 100 mmHg. Oropharyngeal bolus velocity was calculated as 22 cm/sec, increasing to greater than 50 cm/sec in the hypopharynx, later confirmed by Atkinson et al (1957), compared with a peristaltic velocity of 5 - 10 cm/sec. These early cineradiographic studies confirmed that the propulsive force of swallowing was the motion of the tongue and the pharyngeal constrictors. Ardran and Kemp (1952) reported cineradiographic findings in 500 subjects. Although in only two of these was the epiglottis seen to act as a true covervalve over a wide open larynx, they concluded that it did serve useful functions in swallowing. The epiglottis acted as a ledge to receive the bolus and obviated the need for early laryngeal closure by folding on itself, like a hood, over the larynx with its sides forming sloping lateral channels.

Ramsey et al (1955) commented on difficulties in accurate timing but observed earlier cricopharyngeal relaxation with solid boluses which also provoked forceful pharyngeal contractions. Relaxation was noted to be incomplete in some normal swallows and in the erect position swallowed air tended to collect above the bolus in the oropharynx. In this study of 300 subjects, there were also interesting observations of repetitive swallows, during which the glottis remained closed and the epiglottis turned down. Any residuum in the laryngeal vestibule was evacuated only during the final swallow of the series. Christrup (1964) found the point where the bolus passed the posterior palatoglossal fold a useful reference point for timing analysis, with a mean time of 383 msec for the bolus to pass through the cricopharyngeus, but there were problems with imaging in subjects with fat necks, and wide intersubject variations.

Cineradiography also aroused interest in hypopharyngeal webs, many of which are asymptomatic and imaged for only a fraction of a second (Seaman 1967, Nosher et al 1975). Some may be 'false' webs due to transient changes of the postcricoid impression (Pitman and Fraser 1965). A wide range of pharyngeal motility disorders was identified - motor dysfunction, residual filling of recesses, stasis and aspiration or 'silent dysphagia' (Donner and Siegel 1965, Donner 1985). Attempts were made to associate specific radiological findings with particular neurological conditions, eg intention tremor in Parkinsonism, failure of UOS relaxation in brainstem disorders (Silbiger et al 1967).

Ekberg's group found laryngeal aspiration the commonest abnormality (40%) and a possible association of this cause of dysphagia with anatomical differences in some young men (Ekberg and Nylander 1982b, Ekberg and Wahlgren 1985). In patients without dysphagia, there was a 17% incidence of swallowing aberrations, notably abnormal epiglottic tilt, entry of contrast into the laryngeal vestibule and failure of UOS relaxation (Ekberg and Nylander 1982a). The intersubject timing variations also noted by Ramsey et al (1955) led the authors to conclude that each individual may have a unique swallowing pattern but the variability may simply have reflected limitations of the methods used. Ekberg continued his extensive studies over many years to include almost 1,000 dysphagic patients, allowing him to identify less common causes of this symptom such as dysfunction of pharyngeal or cervical oesophageal peristalsis in association with normal UOS function and, in 2%, atony or chalasia of the UOS (Ekberg et al 1985, Ekberg 1987). He could find no radiological evidence of UOS activity outwith the cricopharyngeus muscle (Ekberg and Lindstrom 1987).

Cineradiography, while a very useful tool in the study of the motions of swallowing, is not able to delineate pharyngeal mucosal abnormalities, which may require double contrast and laryngography manoeuvres such as phonation and alterations in respiratory pattern (Gedgaudas-McClees and McClees 1984). A more recent helpful development is videorecording of barium swallow sequences which has largely superseded the original cineradiography techniques (Curtis and Cruess 1984, McIntosh et al 1987). In the oesophageal body, careful fluoroscopy remains adequate (Ott et al 1986) although radiology remains less accurate than endoscopy in the detection of small neoplasms (Grossman et al 1987) particularly in the postcricoid region. Videoradiography is also of limited value in assessing longitudinal movement of individual points of the pharyngeal wall. A study using radio-opaque markers attached by suction to the posterior pharyngeal wall has shown that the extent of such movement is around 2.5 cm

(Palmer et al 1988).

Early attempts to correlate radiological studies of bolus passage with manometric study of pharyngo-oesophageal motility (Atkinson et al 1957, Sokol et al 1966) were limited by the manometric methods used, but were able to confirm that the upper high pressure zone corresponded to the cricopharyngeus and that marked sphincter-on-catheter movement occurred during laryngeal elevation. More recent studies using Gaeltec intraluminal strain gauges (Isberg et al 1985a and b) showed that this movement was asynchronous and could result in erroneous interpretation of pressure recordings. It was concluded that at least three sensors 10 mm apart were necessary for consistent recording in the UOS. Subsequent manofluorometric studies showed that the elevation wave which preceded bolus transit caused a pressure rise in the pharyngo-oesophageal segment (Mendelsohn and McConnel 1987). The conclusion that the ensuing abrupt pressure fall was due to the anterior movement of the posterior plate of the cricoid may not have allowed sufficiently for movement of sensors out of the high pressure zone. Thus, the importance of negative pressure in this area ('hypopharyngeal suction pump') may have been over-emphasised (McConnel 1988). Nonetheless, Hamilton et al (1986a), using a sleeve device in conjunction with videofluroscopy, confirmed that the pressure drop was not merely a movement artifact, despite an average axial displacement of 3 cm. Although manofluorometry is clearly useful in the research of swallowing mechanisms, it is possible that the abnormalities detected in patients with neurological dysphagia (McConnel et al 1988b) could equally well be identified during separate radiological and manometric examinations. In such patients, simple observation of deglutition can also be a valuable means of detecting difficulty in initiation of swallowing, oral incompetence and gross aspiration. Manofluorometric analysis has also been noted to give longer time intervals than those observed in purely radiological studies, a finding which may be due to the presence of the recording catheter (McConnel et al 1988a).

2.3.2 Manometry

Original manometric recordings were made with air-filled balloons linked by an air column to a tambour and smoke-drum (Kronecker and Meltzer 1883). These were superseded first by water-filled balloons, in use till the early 1950s, and then water-filled open ended tubes (Code and Schlegel 1968). Despite the development of miniature intraluminal transducers (Gauer and Gienapp 1950), most investigators continued to use water-filled then water-infused systems linked to external transducers. Pressure recording thus required some movement of fluid or air in or out of the tube which, at high flow rates, could distort the viscus by intraluminal volume changes or induce secondary peristalsis.

Arndorfer et al (1977) developed a low-compliance pneumohydraulic capillary infusion pump which could be used at very low perfusion rates of less than 1 ml/min. Previous systems of greater compliance (dV/dP) had required flow rates of up to 12 ml/min to record accurately proximal oesophageal peaks of 100 mmHg of 1 sec duration (Dodds et al 1972a). In the pharyngo-oesophageal segment such flow was clearly very irritant, producing frequent swallowing or gagging (Dodds et al 1972b). Arndorfer's system maintained reservoir water at a high constant pressure which was reduced to atmospheric pressure by capillary stainless steel tubing with a high resistance to flow. Oesophageal pressure transients had relatively little effect on flow because the reservoir pressure of 1000 mmHg was so much greater. The manometric catheter itself is thus the greatest source of compliance. The post-occlusion pressure rise rate (dP/dt) was in excess of 6000 mmHg/sec with the catheter excluded. With the catheter included, dP/dt was inversely proportional to the internal diameter of the tubing and was greatest for the 0.8 mm internal diameter tube at 840 mmHg/sec, falling sharply where the internal diameter was greater than 1 mm.

Despite this considerable increase in efficiency, it must be remembered that compression of the tube at any point between the tip and the pump produces a pressure change within the fluid column (Wingate 1983) and that the presence of an air bubble has a profoundly deleterious effect on frequency response characteristics (Engler et al 1986). Also, the delay in pressure transmission along the capillary tubing to the external transducers produces a marked drop in frequency response. A further source of artifact is that a perfused catheter measures resistance to stretch ('yield pressure') and thus pressures recorded from both striated and smooth muscle increase directly with catheter diameter (Biancani et al 1973, Kaye and Showalter 1974, Lydon et al 1975) as increase in radial stretch causes elevation of circumferential wall tension. A twofold increase in catheter diameter from 11 to 22 mm caused an increase in measured tonic UOS pressure from 79 to 138 mmHg (Lydon et al 1975).

Dent (1976) developed a sleeve device to overcome another source of error with traditional infused sidehole techniques - sphincter on catheter movement. The sensor is a 5 cm long thin walled rubber sleeve perfused proximally as are the adjacent side-holes on the catheter. The sleeve perfusate is vented distally. The sleeve sensor registers maximum pressure at any point along its length, thus rendering it suitable for prolonged recording of sphincter pressure. Recording side-holes at the upper and lower limits of the sleeve detect non-sphincteric contractions (Linehan et al 1985). The sleeve was later modified for use in the UOS. At an infusion rate of 1 ml/min, the maximum rise rate of the sleeve was only 35 mmHg/sec, compared with a maximum fall rate in excess of 200 mmHg/0.1 sec, while the adjacent side-hole had a maximum rise rate of 400 mmHg/sec (Kahrilas et al 1987a). In addition to the slow rise rate, other disadvantages were the width of the catheter (maximum outer diameter 7 mm) and the necessity for an oral suction device to reduce dry swallowing which interfered with baseline UOS pressure measurement. When the sphincter is on the proximal end of the sleeve, ie closer to the point of perfusion, the tracing returns to a steady baseline more quickly than when the sphincter is on its distal end. This technical limitation is due to the inherent compliance of the sleeve membrane which requires perfusion to tension it (J Dent, personal communication 1987).

The ability of a measuring instrument to follow a changing signal is determined by its frequency response. For critical examination of the waveform, the frequency response of the instrument must be greatly in excess of the repetition frequency of the signal, eg the electrocardiograph has a repetition rate of 1 to 2 Hz but a recording frequency response of 100 Hz is necessary for accurate diagnosis. Also, studies of measurement of blood pressure have shown that catheter tip (intraluminal) transducers are considerably more efficient than fluid-filled catheters with a transducer at its outer end. This is because both the elasticity of the catheter walls and the addition of an incompressible fluid-filled dome drastically reduce the resonant frequency (Brown and Smallwood 1981). The diaphragm displacement of a hydraulically coupled system can be converted into an electrical signal by a variety of methods including thin-film deposition of the strain gauge on a metal diaphragm. The metal diaphragm is coated with a vacuum-deposited insulating film on top of which lie the thinfilm gauges in a Wheatstone bridge configuration. The use of single-crystal silicon allows production of very thin diaphragms (around 20 microns) with very high resonant frequencies (around 100 KHz). A compensation for temperature-sensitivity must, however, be incorporated in this type of transducer, whose sensitivity falls with increasing temperature and whose concomitant expansion can result in temperature drift (Cobbold 1974). A further problem with silicon diaphragm gauges is the difficulty of properly sealing the diaphragm to the catheter. Also, if the diaphragm were to become cracked there would be a potential electrical hazard to the patient.

Before the development of the low compliance infusion pump, Arndorfer's group in Wisconsin introduced intraluminal strain gauges to record pharyngeal peristalsis (Dodds et al 1972b). They were thus able to avoid the problem of gagging secondary to the rapid infusion rates necessary with early perfused systems. Strain gauge measurements yielded similar tonic pressures but greater pharyngeal (up to 420 mmHg) and UOS after-contraction pressures. The duration of pharyngeal contraction decreased from 0.5 to 0.7 sec in the upper pharynx to 0.2 to 0.3 sec in the lower pharynx, with a wave speed of 9 - 25 cm/sec. Thus pharyngeal peristalsis was of considerably greater amplitude and propagation speed and of shorter duration than oesophageal peristalsis. A subsequent report (Dodds et al 1975) confirmed these findings and no difference was observed between wet and dry swallows, although only seven volunteers were studied. The intraluminal strain gauge, with a flat frequency response to 5 KHz, was more than adequate to capture the frequency of pharyngeal transients. The frequency of these pharyngeal waves was thought by Dodds et al (1975) to be 1 - 3 Hz. A later study from the same group (Orlowski et al 1982) used digitisation of peristaltic waves and Fourier transformation to determine frequency content (contribution of harmonics) and wave shape. It was concluded that accuracy up to 48 Hz was required for high-fidelity recording of pharyngeal waves which had a maximum upstroke dP/dt of over 4000 mmHg/sec in some subjects, and an even greater slope on the downstroke, probably due to the functional characteristics of striated muscle. Wave slopes were also much steeper in the striated muscle cervical segment of the tubular oesophagus. The frequency response of polyvinyl catheters is only 1 to 2 Hz which is adequate to capture oesophageal events which have a maximum frequency of 1 Hz (Dodds et al 1976). Also, a pressure rate rise of under 200 mmHg/sec is adequate for the thoracic oesophagus, while the cervical oesophagus requires a dP/dt of greater than 500 mmHg/sec. There is little doubt, therefore, that the optimum recording device for pharyngo-oesophageal motility is a strain gauge assembly. Although adequate for tonic pressure recordings, the sleeve catheter is unlikely to track pharyngeal events accurately, thus limiting its usefulness.

Strain gauge assemblies record pressure independently of position and without the need for elaborate perfusion pumps. Nonetheless, the Arndorfer pneumohydraulic infusion system is the apparatus most widely used in routine manometry today: strain gauge transducers are expensive, fragile and their configuration less flexible than that of fused capillary tubes. Also, pharyngeal recordings are not routinely performed in clinical laboratories and early strain gauge devices were usually limited to three sensors (Dodds 1976). This latter problem was overcome by the development of a circumferentially-sensitive pressure sensor (Kaye et al 1977) designed to take account of the known radial asymmetry of UOS, LOS and peristaltic pressures (Winans 1972 and 1977, Meyer and Castell 1980). The disadvantages of this sensor were its wide diameter (5.1 mm) and a tendency to perforate. A similar sensor, 6.0 mm diameter, was developed in the same year (Weihrauch and Foerster 1977) and subsequently validated by Weihrauch et al (1980a). Rex et al (1988) have compared radially and circumferentially sensitive microtransducers in 30 healthy volunteers. Results showed no significant mid or lower oesophageal motility differences but UOS peak and mean SPT pressures were significantly greater with the three radial sensors, probably because of the greater asymmetry in the upper sphincter. Intrasubject variability was significantly less with the circumferential probe (CV = 0.37).

Manometric results have to date been recorded as analogue tracings on pen and ink or jet recorders. Although secondary computer analysis of digitised transformations of such signals has been described (Feussner et al 1987, De Vault et al 1987, Castell et al 1988, De Bondt et al 1988, McConnel et al 1988a), use of digitised computer waveform analysis of the output signal has been reported in only a few patients (Fradet et al 1988), and will be considered in detail in chapter 4.

The optimum manometric protocol for UOS investigation has yet to be established. In the LOS, comparative studies of continuous or rapid pull throughs with station pull throughs have yielded conflicting results. The UOS poses even greater problems in measurement of tonic pressure because of its greater radial asymmetry. The optimum recording system for swallow analysis also remains to be established.

2.3.3 Intraoesophageal pH Monitoring

Oesophageal pH monitoring was described by Tuttle and Grossman (1958) and Weber and Gregg (1959) following the development of intragastric pH monitoring (Flexner et al 1939, Eyerly and Breuhaus 1939, Rovelstad et al 1952). Early reports suggested pH monitoring to be more accurate than radiology in the diagnosis of GOR (Morgan et al 1963) and the development of glass electrodes with integral, rather than skin, reference electrodes made prolonged recordings more feasible (Spencer 1969). Pattrick (1970) found a poor correlation of acid exposure times with symptoms of reflux - this may have been because the control group largely consisted of patients with duodenal ulceration. Benz et al (1972) found a better correlation with symptoms using either short pH recordings of the distal oesophagus or oesophageal acid perfusion tests (Bernstein and Baker 1958) than with LOS pressure, which was not a useful discriminant, or with acid barium studies (Donner et al 1966), which are a measure of oesophageal sensitivity to the presence of acid rather than a measure of GOR, and are thus frequently positive in asymptomatic subjects. DeMeester's group defined the upper limits of oesophageal exposure to pH less than 4 in 15 normal subjects (Johnson and DeMeester 1974, DeMeester et al 1976). Upper limits of total percentage acid exposure time (4.23%) and of duration of the longest episode (9.4 min) were lower than in previous reports, but there was general agreement that supine reflux was minimal in normal subjects.

Severe oesophagitis was seen only in subjects with supine or combined reflux, but upright reflux occurred in controls, as an exaggeration of physiological postprandial reflux (Kaye 1977). The three factors which reduce recumbent reflux in normal subjects are a diminitution of gastro-oesophageal pressure gradient, a reduction in swallow-induced relaxations and an increase in LOS pressure (Johnson 1980). Where reflux does occur in recumbent asymptomatic subjects, it is associated with transient LOS relaxations (Dent et al 1980) although conversely swallowing also allows small amounts of saliva to neutralise some of the intra-oesophageal acid (Helm et al 1982). At that time, not only were diet and cigarette smoking restricted but also subjects' mobility, as pH values were registered on a chart recorder. Also, the test criterion of symptom correlation may have been misleading, except in the case of atypical symptoms, because of the high incidence of heartburn in the general population. Despite these limitations, pH monitoring was emerging as the 'gold standard' of tests for GOR, as other tests were either too sensitive (acid barium examination), too unreliable (radiology and endoscopic appearances) or too insensitive (LOS manometry). It was, however, apparent that the results of pH monitoring were dependent on test conditions. Irvin and Perez-Avila (1977) performed studies largely in the supine position and with only a fluid intake and showed no association of results with manometry, acid perfusion tests, oesophageal acid clearance or oesophagitis. The low normal AET recorded by Stanciu et al (1977) of $0.17 \pm 0.23\%$ may also have been due to their subjects' supine position. Although Stanciu's group concluded that total time of intraoesophageal pH less than 5 was the best single discriminant, this value was associated with greater inter and intrasubject variations and a level of pH 4 was later generally accepted to be more useful (Wallin and Madsen 1979).

It was also realised that the pattern of reflux might be as important as the total time of acid exposure (which does not in any case reflect the amount of acid material refluxed). Oesophageal acid clearance is more efficient in the upright position, making upright reflux less injurious to oesophageal epithelium, while impaired acid clearance during sleep may contribute to development of pulmonary symptoms (Johnson 1980). The major mechanism of oesophageal clearance is primary peristalsis (Dent et al 1980). Impaired acid clearance is thus associated with motor coordination and in children with the prone position (Boix-Ochoa et al 1980). The original normal values obtained by DeMeester in 15 subjects continued to be reported (DeMeester et al 1980) and were used to compile a weighted scoring system.

A major advance was made with the development of portable methods of pH registration, allowing subjects for the first time to be studied as ambulant outpatients (Falor et al 1980). Using a pH sensitive radiotelemetry capsule and a portable analogue tape recorder Branicki et al (1982) demonstrated significantly greater oesophageal AETs at home than when in hospital in all subjects. In the 10 normal volunteers, however, the upper limit of normal total AET was less than in patients, although the principal results reported were the median number and duration of reflux episodes. The authors later described a frequency duration index (Branicki et al 1984) for the evaluation of pH recordings, based on these variables but this failed to gain acceptance probably because of its complexity compared with the simplicity of the automatic analysis of the new computer-based pH recording methods (Pezzuoli et al 1983, Vitale et al 1983, Sadek et al 1984). These comprised a radiotelemetry or glass electrode linked to a portable microcomputer recorder which stored pH data digitally but could also yield a graph of pH throughout recording.

The most popular electrodes currently in use are glass or mono-crystalline antimony, which have a linear pH response to pH 8 or greater. A sampling rate of at least 10/min for these electrodes is required (preferably 60/min), and a pH accuracy of 0.5 units (Emde et al 1987). Glass electrodes need to be protected from drying between studies, and electrodes require careful calibration in solutions of known pH before use. These newer methods applied to larger numbers of asymptomatic subjects on a pH restricted diet gave total AETs similar to those of DeMeester if used on outpatients (Vitale et al 1984) or lower where controls were either hospitalised (Johansson et al 1986) or had no abnormality on a variety of oesophageal tests (Fink and McCallum 1984).

It was concluded that endoscopy should be used in conjunction with pH monitoring as some patients with oesophagitis had results within the normal range (Vitale et al 1984) and that shorter, postprandial study periods might be as useful as prolonged 24 hour recordings (Fink and McCallum 1984). It was later shown that results were independent of age (Spence et al 1985) and smoking (Schindlbeck et al 1987a) but varied with electrode site, being one third lower when recorded at 15 cm than at 5 cm above the LOS (Johansson et al 1986). Schlesinger et al (1985) were the first to record a wide normal range with an upper limit of normal total AET of 8.6% in hospitalised subjects on pH restricted diet (based on X + 2 SD), and confirmed the occurrence of negative tests in the presence of oesophagitis. The most consistent predictive variables were the total AET and the number of episodes greater than 5 minutes. Only 48% of patients with typical reflux symptoms had abnormal results and it was proposed that the insensitivity might be due to performance of the test on hospitalised subjects. Schlesinger's normal values were later criticised as having been obtained from inappropriately selected control subjects (Pujol et al 1988), although other more recent results have supported his finding of a wide range of normal oesophageal AET.

Some of the variation in normal values among different studies may also have been related to the recording system used (Ward et al 1986) and the accuracy of its calibration (Ask et al 1986). Differences in awareness of device may have caused different dry-swallow rates and thus of salivary neutralisation, and difficulty in determining of the onset and end of individual episodes yielded variations in the number of reflux episodes reported. The symptom index was devised to overcome some of these problems and represents the ratio of the number of occurrences of a symptom at pH less than 4, divided by the total number of times the symptom is reported (Wiener et al 1988b). This approach has advantages over simple classification of results as normal or abnormal, as in such dichotomy the definition of abnormality by some other criterion (usually the presence of 'typical' symptoms) is clearly implicit. The symptom index also provides for the assessment of atypical symptoms of GOR such as chest pain (Janssens et al 1986) or hoarseness but does not reflect the occurrence of asymptomatic reflux episodes and the variable correlation of heartburn with reflux episodes (Helm et al 1988). Ward et al (1986) also considered that pH monitoring was inferior to endoscopy in the diagnosis of oesophageal mucosal changes and that the role of pH monitoring was to determine whether and when abnormal GOR occurred, and to establish its temporal association with the patient's symptoms. It was later shown, however, that AET was related to the presence of oesophagitis (Rokkas and Sladen 1988, Pujol et al 1988). pH monitoring was also used to establish the importance of daytime reflux, especially post prandial reflux and acid clearance, in the aetiology of oesophagitis (De Caestecker et al 1987).

The problem of 'abnormality' was later addressed by Schindlbeck et al (1987b) who used receiver-operating characteristic analysis to discriminate between controls and GOR patients. A 93% sensitivity and specificity was obtained if subjects were classified as normal only if they had both an upright AET less than 10.5% and a supine AET less than 6%. While all patients against whom these criteria of normality were tested had 'typical symptoms' of GOR, over half had normal endoscopy. Also the upper end of the normal range was 45% which would be regarded by most workers as unacceptably high for a control subject, although the corollary that AETs do not conform to a Gaussian distribution had previously been overlooked by most investigators who had relied on parametric methods of data analysis. Because of this, Johnsson et al (1987) used the 95th percentile of pH monitoring results from 50 normal subjects, which was 3.4% for total AET less than pH 4, (4.6% ambulant) although five prospective asymptomatic controls were found at prior endoscopy to have oesophageal abnormalities and were excluded from the study.

These exclusions may well explain the marked discrepancy between Johnsson's results and those of Schindlbeck et al, in view of the positive skew of the latter's data. There is a high incidence of histological oesophageal abnormalities in asymptomatic subjects, 10% of whom may have acute inflammatory infiltrate and up to 30% of whom show epithelial thickening or basal cell hyperplasia (Behar et al 1976) and exclusion of such individuals from a control group may markedly influence results. Intrasubject variability is a further factor contributing to the wide range of reported normal values (Johnsson and Joelsson 1988, Shaker et al 1988b, Wiener et al 1988a). Two recent studies have also disclosed unexpectedly high levels of acid exposure in normal subjects (Shaker et al 1988b, Smout et al 1988), apparently independent of dietary intake. Shaker's total AET of 6 $\pm$ 5% in normal subjects, for example, yielded a false positive rate of 14 to 21% for a diagnostic sensitivity of 75%, ie there was considerable overlap of subject groups on receiver-operating-characteristic analysis. Use of standard deviations to describe the data may not have been appropriate, but these findings emphasise the point that each centre must acquire its own normal data (Emde et al 1987).

The clinical applications of pH monitoring have become more specific as the difficulty of discriminating between physiological and pathological reflux by this method alone has become more appreciated. The investigation is undoubtedly useful in the evaluation of atypical symptoms, particularly if episodic, or typical symptoms with normal endoscopy (Donald et al 1987). It can also identify precipitating factors of GOR, assess medical and surgical therapy and remains, despite the remaining problems, the 'gold standard' for the diagnosis of GOR (Evans 1987).

3. LARYNGO-PHARYNGEAL DISORDERS

3.1 GLOBUS PHARYNGIS

'O how this mother swells up toward my heart!
Hysterica passio - down, thou climbing sorrow,
Thy element's below!' King Lear, Act II, scene iv.

'But thy throat is shut and dried, and thy heart against thy side
Hammers: 'Fear, O Little Hunter - this is Fear!' Kipling 1895.

Globus sensation, a feeling of something in the throat, from the Latin globus, a ball, was observed by Hippocrates and constituted the graphic 'suffocation of the mother' which was known to Shakespeare and was one of the definitive symptoms of hysteria in the 17th century (Brain 1963, Merskey 1986). Mild forms of globus sensation occur in 35% of males and 53% of females in the general population (Thompson and Heaton 1982) and globus accounts for 4% of present-day laryngological referrals (Moloy and Charter 1982). A wide variety of organic explanations has been proposed to account for these more severe or persistent forms of the sensation which is up to three times more common in women than men under the age of 50, but of equal sex incidence over 50 years (Moloy and Charter 1982). During the 1950s, interest centred on hypertrophy of the lingual tonsils and anterior cervical osteophytes (Rigby 1952, Tremble 1956). Kiviranta (1957) found large lingual tonsils in 40% of globus patients, but there has been no attempt at controlled quantification of lingual tonsillar size and an uncontrolled trial of lingual tonsillectomy in 23 globus patients produced symptom relief in only four (Miyake and Matsuzaki 1970).

Similarly, although granular pharyngitis (Tremble 1959) and sinusitis (Mills 1956) have been associated with globus, the incidence of globus in these common conditions is unknown. Styloid process elongation is also an occasional concomitant of globus but it has been shown that fewer than 10% of patients with this abnormality experience globus sensation (Kaufman et al 1970). Also, although there have been several reports of globus and cervical dysphagia due to osteophytes (Zahn 1905, Mosher 1926, Maran and Jacobson 1971, Counter 1977) the high incidence of cervical spondylosis in the general population (Pallis et al 1954, Irvine et al 1965) makes a causative association difficult to establish. In consequence, several authors have sought to attribute their patients' globus sensation to a wide variety of observed minor physical abnormalities. Rigby (1952) included such varied causes as diabetes, rectal polyps and eye strain and concluded that the improvement seen following the correction of such problems made the term 'globus hystericus' inappropriate, but did not address the problem of why some patients with these conditions should experience globus sensation. Henry (1958), on the other hand, who also described a variety of associated findings including pharyngitis, spondylitis, oesophagitis and foreign body trauma, concluded that in many cases there was a 'varying element of truth' in regarding globus patients as neurotic. Nishijima et al (1984) found many different diseases, including gallstones, hepatitis and colonic carcinoma in one third of 290 globus patients referred to a cancer centre. While some of the more proximal lesions such as peptic ulcer and oesophagitis may have had causal associations with the presenting complaint, the more distal findings may in some cases have been coincidental or have induced some form of psychological alteration which resulted in a globus feeling.

Overclosure of the bite was reported as a cause of globus by Campbell (1962) who described the secondary falling back of the base of the tongue as one of the factors producing cramp-like pains on swallowing. A placebo-controlled trial of occlusal adjustment in a selected group of globus patients, all but one with symptoms referable to the temporomandibular joint, showed that the use of splints caused an improvement in six of 13 patients (Kirveskari and Puhakka 1985). A placebo response was, however, noted in three of nine patients treated by mock adjustment and the importance of psychological factors in temporomandibular joint dysfunction is now so well recognised (Thomson 1982) that the association of globus with this syndrome may well be an indirect one.

The most popular organic aetiological theory in recent years has been that globus is an atypical manifestation of GOR. Henry (1958) noted oesophagitis in 50% of globus patients undergoing endoscopy and Steinmann (1961) found radiological evidence of a hiatus hernia in 12 of 14 patients with globus which was resistant to treatment. The large radiological series of Malcomson (1966 and 1968) showed that 63% of globus patients had a primary lesion at or below the gastro-oesophageal junction, two thirds of which were hiatus herniae and the remainder were peptic ulcers. Malcomson commented on the large percentage of afferent fibres in the subdiaphragmatic vagus and proposed that either the association of these distal lesions arose through referred sensation, or by an increase in visceromotor tone resulting from an increase in dry swallowing in response to a feeling of something in the throat. Breuninger (1974) also noted a compulsive throat clearing in globus sensation, with secondary voice changes and that dysphonia could become the principal symptom in patients heavily dependent on voice use. The referred sensation theory was supported by previous experimental work on oesophageal balloon distension (Polland and Bloomfield 1931) which showed the suprasternal notch was a site of predilection for referred pain, and that the sensation produced sometimes resembled heartburn but could also be the feeling of a 'lump'.

Delahunty and Ardran (1970) used the acid barium investigation described by Donner et al (1966) to investigate 25 globus patients and found that midoesophageal motility abnormalities occurred in 22 patients which the authors interpreted as evidence of oesophagitis. Over half of the patients studied, however, had symptoms strongly suggestive of GOR, with corresponding barium meal findings. Only one of the 22 failed to respond to an uncontrolled trial of an antacid regime. It was proposed that the presence of oesophagitis provoked secondary oesophageal dysmotility which, in turn, induced globus sensation. A similar acid barium study of 12 patients (Cherry et al 1970) demonstrated a hiatus hernia in only three, but 11 had positive acid barium results. Three also had oesophagohypopharyngeal reflux, and in 10 patients globus could be reproduced by distal oesophageal acid perfusion. All 12 responded to an uncontrolled antacid regime and most admitted to prior frequent antacid use when questioned retrospectively after the study. Freeland et al (1974) were able to follow a much larger cohort of 124 globus patients for up to three years. All had evidence of a hiatus hernia and/or acid sensitivity of the oesophagus. Erythema of the arytenoids was noted in 33 patients and the response of this group to an uncontrolled trial of antacid therapy was even greater than the 77% response in the group as a whole. As an alternative to referred sensation, it was proposed that direct contact of acid with the hypopharynx and posterior larynx might be responsible for the patients' symptoms. Posterior laryngitis is considered further in 3.2. Although larger than the two previous studies, the series reported by Freeland et al shared the problems of reliance on acid barium techniques to diagnose reflux and on clinical response to an uncontrolled trial of antacid therapy to establish an association of globus and GOR.

Mair et al (1974) reported the two year follow-up of an unselected series of 77 consecutive globus patients, and found interesting sex differences both in radiological findings and in the response to treatment. Overall, only 46% of patients had a positive neutral or acid barium investigations and it was thought some findings may have been incidental. Endoscopy was performed in 23 selected patients (Mair et al 1973) and oesophagitis found in 10 patients. In 60% of the female patients, but only 36% of males, there was no radiological abnormality. Moreover, the therapeutic success rate at 2 year follow-up was twice as great in females (53%) as males, irrespective of radiological findings but the sensation had completely disappeared in less than 12% of patients. Moloy and Charter (1982) also noted that over 20% of globus patients were resistant to a variety of treatments. The response to antireflux therapy was not sex-related and was again independent of the presence of GOR and of the effects on reflux symptoms.

The finding that globus was not associated with an increased incidence of heartburn (Moloy and Charter 1982, Thompson and Heaton 1982) also supported the suggestion that the association of globus and GOR may be no more than the chance occurrence of two common phenomena in one individual. Despite this conclusion, the earlier studies and a number of anecdotal reports of GOR in association with head and neck symptoms (Hallewell and Cole 1970, Weisskopf 1981) led Bain et al (1983) to propose that as the accurate diagnosis of GOR required expensive tests such as pH monitoring, the best plan of management was to treat patients with suspected atypical symptoms of reflux with an antacid regime, and to investigate further only the non-responders.

Attempts have been made to resolve the conflicting reports of the association of globus and GOR by proposing two subgroups of patients - one with primarily psychological problems, the other in whom globus represents an atypical reflux symptom (Anonymous 1982). Thus the varying incidence of GOR in globus patients can be attributed to differences in patient selection. It has long been recognised that physical findings in globus are heterogeneous, however, and such a dichotomy is likely to prove an over-simplification. Although globus is a sensory symptom, without true dysphagia, many patients perceive difficulties in swallowing, particularly between meals, ie during 'dry' saliva swallows (Schatzki 1964). There has been much controversy as to whether the sensation of globus arises from a primary sensory or motor abnormality. Historical motor explanations of globus include strap muscle spasm and retrograde motion of the oesophagus (Darwin 1796). Munro (1811) writes 'hysterical women are also subject to a spasmodic contraction of the gullet ... even young women in whom there is no Globus Hystericus'. Rosenheim (1895) was unable to identify spasm endoscopically and described the immediate relief of symptoms during eating or drinking. He attributed globus sensation to a primary hyperaesthesia of the mucous membranes and concluded that any spasm present was a secondary phenomenon, a feeling supported by some contemporary workers who felt that the absence of true dysphagia in globus made UOS spasm unlikely. In contrast, Killian (1907) considered that cricopharyngeal spasm was indeed the cause of globus and Antoni (1923) felt that this spasm was a neurotic reflex and only part of a more general 'visceralen Neurose'. Antoni also acknowledged that in some patients globus was a symptom of organic abdominal disease. Jacobson (1924) reported two atypical cases of globus with radiological spasm of the oesophageal body. One appeared to have moderately severe claustro- and agarophobia and the other had previously been treated for neuraesthenia and tuberculosis. Although Jacobson's findings led him to conclude that the primary pathology of globus was spasm, he did not exclude a secondary hyperaesthesia of the striated muscle and expressed a wish for confirmatory studies by others.

These were not forthcoming. Kronfeld (1934) felt that globus represented a synthesis of both types of 'Oesophagus-neurosen', ie sensory hyperaesthesia and reflex spasm. Lindsay (1955), who agreed that cricopharyngeal spasm was probably present, felt that the hypertonicity could not be detected by contemporary radiographic methods and that even in cases with dysphagia, the appearances could be normal. Welin (1939) observed slow return of the epiglottis during a radiological study of swallowing in five patients with globus sensation and a similar abnormality was claimed by Curtis and Cruess (1984) to be 10 times more common in globus patients than in a control group, but only two subjects in each group in fact demonstrated this abnormality. Hannig et al (1987) identified abnormality in pharyngeal movement cineradiographically and felt that this observation warranted further observation. Schatzki (1964) proposed that repeated dry swallowing in tense individuals with heightened bodily awareness might be an important cause of globus in some patients. This idea was expanded by Gray (1983) who described 'inferior constriction strain swallows' in globus. These swallows were performed without the normal epiglottic tilt, with reduced hyoid elevation and air distension of the upper oesophagus causing cricopharyngeal spasm. This type of swallow might be initiated by an increased awareness of contact between the epiglottis and slightly inflamed lingual tonsils following an upper respiratory infection and, like Schatzki, Gray believed it could provoke a vicious circle of saliva swallows, with saliva or mucus being produced to lubricate these, causing further exacerbation. Increased frequency of swallows led to reduction in interswallow interval, so that periods of failed UOS relaxation, or spasm, ensued. Despite the detailed radiological description of the 'strain swallow' it would appear that the only subject actually investigated was the author himself. In a review of radiological findings in more than 300 globus patients, Ardran (1982) found no abormality in one third, GOR with or without hiatus hernia in a further third and poor clearance of barium in the remainder. In 5% of patients there were numerous radiological abnormalities in the pharynx including osteophytes, diverticula and calcified stylohyoid ligaments which were considered to be incidental in most instances. Like Gray, Ardran also proposed a 'vicious circle' mechanism in globus, but he related this cycle to reflux and felt that the reduction in peristaltic amplitude secondary to reflux produced an increase in swallowing frequency. Resultant deglutitive inhibition was thought further to impair acid clearance. The ingestion of HCl, however, was required to elicit GOR or impaired acid clearance in an unspecified number of subjects, a manoeuvre which may have considerably influenced the results of the study. Oesophageal acid clearance can now be assessed more physiologically during prolonged pH monitoring studies.

The first manometric investigation of globus was carried out in 1970 by Caldarelli et al, who studied 10 patients with a water-filled catheter. Tonic UOS pressures were not significantly different from those of six control subjects, but UOS after-contraction was of reduced amplitude. The less variable swallow parameters in controls led Caldarelli to propose that cricopharyngeal function was 'restricted' in globus patients although this conclusion may not have been justified in view of the small number of subjects studied. Four years later Watson and Sullivan (1974) used a triple-lumen perfused catheter in a study of nine globus patients and 22 controls, who included patients with GOR, achalasia and unexplained chest or epigastric pain. Levels of UOS pressure recorded in the globus group were significantly higher than those of controls (70 to 140 mmHg) and appeared to be so high (140 to 220 mmHg) as to compromise UOS circulation (Christensen 1983). Allowance for UOS asymmetry was made by rotating the catheter while in the sphincter, but the findings were unconfirmed (Flores et al 1981) and may have been influenced by the selection of the small number of globus patients studied, the heterogeneous control group and the methods used. Flores et al used a similar catheter and perfusion rate (0.4 ml/min) to Watson and Sullivan but recorded resting UOS pressures of only 9 to 31 mmHg in 12 globus patients, compared with an upper limit of normal of 50 mmHg. The discrepancy of UOS pressures between the two series reflects the limitations of the available manometric technology. Flores found slight elevations of intraoesophageal resting pressure in 10 patients and described spontaneous, repetitive low amplitude contractions in the oesophageal body in nine patients although no control data or diagnostic criteria for these findings were reported, and the age range of the 12 subjects studied (20 to 73 years) was considerable. Abnormalities of peristalsis, but not UOS tonic pressure, were identified in four of 18 globus patients in a study using intraluminal strain gauges (Linsell et al 1987) and it is possible that such findings initiate reflex changes in sensation in the cervical region.

Although clearly not yet fully defined, it remains possible that motor abnormalities in globus represent phenomena secondary to psychological factors. The classical theory that globus was a 'hysterical' phenomenon was, after all, based on centuries of clinical observation and it is not only the female preponderance which has stood the test of time. The comment 'absolutely characteristic was the rather anxious introspective personality that these patients display' comes from a writer who believes that 60% of cases are due to GOR (Batch 1988). Globus patients are very readily identified clinically, even at the outset of consultation. Patients themselves, perhaps in response to occasional reports in the popular press (Edwards 1988), frequently ask 'could it be nerves?' The concluding paragraphs of this section will attempt to answer this question.

The ancients explained the propensity of females to certain psychological conditions by attributing them to a uterine origin - hence 'hysteria' from the Greek hystera, womb. The uterus ('mother') was thought to migrate and produce symptoms in women, although presumably not exclusively so, in view of Lear's dramatic utterance. The semantic ambiguity and pejorative overtones which have since surrounded the term 'hysteria' have limited its usefulness and threatened its viability (Lloyd 1986, Taylor 1986). Hysteria was the principal condition studied in the development of psychoanalytic theory by Freud who considered that hysterical symptoms arose from the conversion of repressed ideas. Ferenczi (1926) proposed a peripheral 'materialisation' of the repressed idea, claiming that a palpable muscular ball developed in globus patients as a foreign body with erotic significance in response to a subconscious desire for oral sex. The psychodynamic symbolism of globus includes not only sexual but also oral and incorporation phenomena. Glaser and Engel (1977) related globus to the close association of feeding and crying in infancy which, they believed, provided a basis for a sensation of a lump in the throat during inhibited crying. The impulse to cry represented the earliest means of re-establishing a disrupted relationship with the feeding person and its repression may have indicated an unwillingness to accept the loss.

However appealing these theories may be to the psychoanalyst, the frequency of globus both in the general population and in the hospital setting suggests that the location of globus is unlikely to hold a mysterious significance. The American classification of hysteria (Diagnostic and Statistical Manual 1980) now includes three categories - conversion disorder, somatization disorder and histrionic personality. These are clearly distinct: only 5 to 20% of those with conversion disorders are reported to have a histrionic personality (Ford and Folks 1985). A review of general medical patients has suggested that over 20% have at some time experienced conversion symptoms (Lazare 1981). Although globus was described by Marmor (1953) as ranking with anorexia and bulimia as 'bywords in the symptomatology of hysteria', globus is today rarely seen in psychiatric practice and patients continue to be referred to otolaryngologists for the exclusion of an organic basis for the symptom. The possibility of a secondary psychological disturbance due to fear of cancer must, therefore, also be borne in mind (Wildhagen 1965).

Modern theories of conversion reaction include manipulation, learned behaviour and defective communication skills resulting in non-verbal 'pantomime' communication. In order to qualify as a conversion symptom, the involved organ must be under voluntary control (Chodoff and Lyons 1958, Ford and Folks 1985). Taylor (1986) argues that hysteria is only a disease by medical consensus and that patients are simply engaged in the 'enactment of distress'. There is continued debate about the personality associations, concurrent somatic or psychological pathology and diagnostic stability of hysteria, largely due to the incomparability of subjects in different studies which are mostly of psychiatric or neurological patients (Ziegler at al 1960, Slater 1965). Many patients suffer from diseases which may themselves produce conversion reactions, denial or even personality change

(Lewis 1975, Wilson-Barnett and Trimble 1985, Lloyd 1986). In some patients conversion may be a defence against depression which is a concomitant finding in 8 to 88% of cases. The picture is further clouded by the fact that many patients' symptoms constitute phenomena which are themselves intrusive life-events, eg paralysis or convulsions.

In a recent study, globus was the fourth most discriminating symptom of conversion disorder after vomiting, aphonia and painful extremities (Othmer and DeSousa 1985) and globus also appears to fulfil the criteria of the Diagnostic and Statistical Manual (1980) for conversion disorder. The patient may experience alteration in swallowing (Schatzki 1964) or speaking (Breuninger 1974), may volunteer a psychological event at the onset of the symptom and derives opportunity for support (hospital attendance). Nonetheless, there have been surprisingly few studies of psychological aspects of globus. Behaviour, family and antidepressant therapy are reported to be of benefit in a few isolated case reports (Kaplan and Evans 1978, Solyom and Sookman 1980, Oberfield 1981, Brown et al 1986). The previous psychometric studies of globus have yielded conflicting results. Lehtinen and Puhakka (1976), in a study of 20 globus patients, found depressive and obsessive characteristics in 11 females, while males were similar to controls. There also appeared to be an increased incidence of predisposing life events and of sexual problems in females but many of the findings were based on subjective impressions. Pratt et al (1976) applied the Minnesota Multiphasic Personality Inventory to 99 globus patients, and found a higher incidence of depression and hypochondriasis in the 23 male patients.

In summary, therefore, the results of psychological investigations are few and conflicting. Even if psychological factors are established in globus patients, by what mechanisms might such variables produce the sensation? As globus is a sensory symptom, it is possible that its genesis requires no more than an alteration in afferent input from the hypopharyngeal area - the 'hyperaesthetic' theory of Rosenheim (1895). It has been shown recently (Richter et al 1986a) that patients with recurrent non-cardiac chest pain have reduced pain thresholds for oesophageal balloon distension and indeed the suggestion that oesophageal pain might also result from hyperaesthesia was first made a century ago by Osgood (1889). A similar alteration in sensory awareness may operate in globus patients but it is difficult to assess objectively such an alteration in sensation. An alternative explanation is that the sensation itself is no more severe in patients seeking medical advice on globus than in the general population, but that its presence is perceived to be more troublesome as suggested by Schatzki (1964). Pennebaker (1982) provides much evidence that bodily sensations compete with external cues for an individual's attention and has indicated that self-focussed attention may be one aspect of patients whom he terms 'symptom reporters'. Some globus patients may also be classed as having 'functional somatic symptoms' (Kellner 1985), ie physical symptoms of obscure aetiology despite history, examination and investigation, where hypochondriasis has been excluded.

Conversely, globus may be associated with demonstrable alteration in motor function - as suggested by Ferenczi (1926) in his 'materialisation' hypothesis. Jacobson (1927) associated symptoms of oesophageal spasm with stress-induced distal oesophageal manometric contractions. Faulkner (1940) and Faulkner et al (1941) demonstrated the association of acute emotional stress and oesophageal spasm during endoscopic and radiological studies of a small number of patients. Wolf and Almy (1949) observed radiological uncoordinated contractions and prolonged oesophageal transit times when patients discussed emotionally charged life-situations and concluded that LOS achalasia (cardiospasm) may occur as part of a biological reaction to stress and be partially reversible in its early stages. Similarly, Rubin et al (1962) found a significant increase of nonpropulsive activity of the oesophageal body in five volunteers while 'affectively charged' material was being discussed. The finding of an association of oesophageal spasm and stress is paradoxical, as it is the parasympathetic limb of the autonomic nervous system which induces contraction of the gastrointestinal tract (Schuster 1983a). The increase in symptoms in patients with oesophageal motor disorders during stress was thought by Cohen and Snape (1977) to be related to altered patterns of food ingestion, as the oesophagus is sensitive to bolus size, temperature and consistency.

There have been several recent manometric studies of functional aspects of oesophageal motor disorders. Clouse and Eckert (1986) found that 19% of patients with oesophageal contraction abnormalites including nutcracker oesophagus and diffuse oesophageal spasm had associated large bowel symptoms and postulated that functional gastrointestinal symptoms might represent a diffuse neuromuscular derangement in the gastrointestinal tract. At the same time, a study by Richter et al (1986b) showed that patients with both nutcracker oesophagus and irritable bowel syndrome differed significantly from controls on scales of gastrointestinal susceptibility and somatic anxiety of the Millon Behavioral Health Inventory. Irritable bowel patients appeared to have a more generalised disorder as they showed increased depression and hypochondriasis scores. It was concluded that emotional factors might modulate pain perception in the nutcracker oesophagus. Stacher (1983) demonstrated that acoustic stimuli at 1 KHz of around 90 decibels could elicit oesophageal tertiary contractions which were thought to represent a defence reaction to intense exogenous stimuli. There was no evidence, however, that such experimental responses could lead to organic disease. Young et al (1987) did not confirm the presence of tertiary contractions during stress of 14 healthy volunteers, but instead identified increased peristaltic amplitude as the primary response of the oesophagus to stress in the forms of 100 decibel white noise and problem-solving tasks. The group later reported a similar finding in patients with oesophageal chest pain (Anderson et al 1989).

Clouse and Lustman (1983) suggested that patients with a variety of psychiatric illnesses showed specific oesophageal contraction abnormalities. Depression, anxiety and somatisation in this group were identified by a structured psychiatric diagnostic interview, although the relevance of these to the manometric findings, and to the patients' experience of chest pain, remained unclear. A placebo controlled study by Clouse et al (1987) of a low dose antidepressant (trazodone) in patients with symptomatic contraction abnormalities showed a significant reduction in overall oesophageal symptoms in the treated group. A striking placebo response in the reduction of chest pain was also noted, and there was no correlation of symptomatic improvement with manometric findings. The lack of manometric improvement suggested that trazodone, which has anxiolytic activity, affected the distressing nature of the symptoms more than their actual occurrence and that the primary effect may have been on symptom-reporting.

It has been reported (Cook et al 1987) that the stress of a dichotic listening test can cause elevations of UOS pressure by up to 20 mmHg. It is possible that such effects contribute to the generation of globus sensation. If transitory, they might also provide an explanation for the conflicting reports of UOS tonic pressure in globus sensation. The dichotic listening test has also been shown to induce noncardiac chest pain in both normal subjects and in patients with a variety of oesophageal disorders (Kennedy-Symonds et al 1988). There is, therefore, experimental evidence to support a similarity in stress responsiveness between the striated and the smooth muscle of the oesophagus which may have therapeutic implications for globus patients. Schuster (1983b) has used biofeedback techniques to induce reduction in LOS pressure and a similar approach might be of benefit in globus.

In conclusion, the aetiology of globus remains ill-understood. Investigations of organic theories have yielded conflicting results and the results of uncontrolled therapeutic trials have been over-emphasised in the literature. Globus sensation, like many other symptoms which may have a psychological component such as headache, tinnitus, and noncardiac chest pain, may be present in a heterogeneous group of patients. In other functional gastrointestinal diseases, psychological features, personality traits, psychiatric illness and acute stress are known to be relevant. Some or all of these may influence the patient's perception or reporting of globus as a distressing symptom.

3:2 POSTERIOR LARYNGITIS

Reflux of gastric acid was first suggested as an aetiological factor in laryngeal disease by Cherry and Margulies (1968) whose radiological study of three patients with refractory contact ulcer of the larynx showed that all had reflux oesophagitis and oesophagopharyngeal reflux. Later experiments demonstrated the production of laryngeal ulcers by the application of gastric acid to the vocal cords of two dogs (Delahunty and Cherry 1968). Delahunty (1972) then extended the spectrum of acid-associated laryngeal pathology to include pachydermia (hyperplasia with oedema and inflammation) of the posterior third of the larynx. He reported nine patients with posterior third inflammation, all with strongly positive acid barium studies and a good response to antacid regimes. Histological changes identified were of epithelial proliferation with areas of keratosis and parakeratosis. At the same time there were also uncontrolled studies of GOR or hiatus hernia with secondary UOS dysfunction in the majority of patients with pharyngeal pouch (Delahunty et al 1971, Smiley at al 1970). A more recent retrospective controlled study has reported a 39% incidence of hiatus hernia in pharyngeal pouch patients, compared with a 16% incidence in a control group of patients with head and neck malignancy (Gage-White 1988).

In pharyngeal pouch patients it was thought that GOR produced cricopharyngeal spasm (Delahunty et al 1971) but other ENT diseases were thought to arise from GOR in association with UOS incompetence. The resultant oesophagopharyngeal reflux was thought by Chodosh (1977) to cause hoarseness, webs, globus, dysphagia, otalgia and laryngospasm. Chodosh himself, however, commented on his failure to use specialised investigations and his paper is, in effect, an impressionistic report of nine cases. Several other contemporary studies report GOR as an aetiological factor in pharyngitis, laryngeal ulcer or granuloma, posterior laryngitis or otherwise inexplicable hoarseness (Hallewell and Cole 1970, Goldberg et al 1978, Ward et al 1980, Ward and Berci 1982, Bain et al 1983, Kambic and Radsel 1984). All of these relied on radiological methods to diagnose GOR, or on clinical features, ie history of heartburn or a response to an antacid regime. In the case report of Goldberg et al (1978), the association with GOR was based on the patient's response to hiatal repair and the histological similarity of the laryngeal granuloma to inflammatory pseudopolyp of the oesophagus. Ward and Berci (1982) considered that oesophagopharyngeal reflux produced a vicious circle of hypopharyngeal irritation with harsh throat clearing and coughing which traumatised the vocal cords and contributed to laryngeal disease. A possible functional basis for symptoms was dismissed on account of the response to antacid measures - but these were, unfortunately, uncontrolled and included cessation of smoking, clearly an independent laryngeal irritant. Pearlman et al (1988) identified only 25 patients with both cervical symptoms and oesophagitis in a group of 379 patients undergoing oesophagoscopy for GOR in a four year period. Little et al (1985) reported a case of subglottic stenosis controlled by antacids and later demonstrated in canine experiments that gastric acid applied to mucosal lesions produced subglottic stenosis. Like the canine experiments of Delahunty and Cherry (1968), however, the findings bear a questionable relationship to clinical pathophysiology in all but the most exceptional cases, although Wynne et al (1981) demonstrated that gastric contents caused marked mucosal damage in the mouse trachea even when the amount aspirated was too small to produce a clinically significant pneumonia. Gaynor (1988) concluded from similar studies in the rabbit that the exposure time was less critical than the pH of the experimental solution applied.

In the lower respiratory tract, there was interest in the role of GOR in the aetiology of asthma. Mays (1976) found radiological reflux in 13 of 48 patients with severe asthma, a significantly greater incidence than that in controls. Several mechanisms were later proposed whereby GOR might be associated with pulmonary disease. Micro-aspiration may cause stimulation of upper airway receptors and overt macro-aspiration can induce chemical pneumonitis. GOR may also induce reflex bronchospasm by stimulation of oesophageal receptors and bronchospasm can in turn induce reflux by increasing the transdiaphragmatic pressure. Finally, some bronchodilators can induce reflux by effects on LOS pressure (Boyle et al 1985, Barish et al 1985). Probably 50 to 60% of asthmatics suffer from reflux (Goldman and Bennett 1988) but radioisotope studies have failed to demonstrate micro-aspiration. Confirmation of aspiration by pH monitoring, ie pH drop followed by acid taste, cough or wheeze, was possible in only 8 of 48 patients with clinically suspected aspiration (Pellegrini et al 1979). Nagel et al (1988) were also unable to demonstrate differences in the amount or pattern of GOR on pH monitoring between asthmatics experiencing nocturnal reduction in peak expiratory flow rates ('morning dipping') and those without morning dipping. Peters et al (1986) found no difference in the incidence of GOR between extrinsic and intrinsic asthmatics and observed a three times greater incidence of reflux in patients on theophylline and sympathomimetic medication. GOR and asthma may, therefore, exacerbate each other in a vicious circle.

A preliminary investigation of reflux in intrinsic asthma revealed white plaques in the posterior larynx of 92% of reflux patients and 76% of patients with reflux and asthma (Larrain et al 1981). In only three patients were biopsies obtained. The changes of hyperkeratotic stratified squamous epithelium were thought to be due to GOR but subsequent doubts about the normal epithelium in this area of the adult larynx precluded further publication (C E Pope, personal communication 1988). A recent study of epithelial distribution in the foetal larynx found both ciliated respiratory and squamous epithelium in supraglottic, glottic and subglottic specimens. Thus squamous epithelium is a normal finding in the extraglottic larynx and does not represent a metaplastic change caused by trauma as had previously been thought (Stafford and Davies 1988).

There have been a few other studies using pH monitoring to investigate so-called 'acid laryngitis'. Wiener et al (1986a) reported 14 consecutive patients with chronic hoarseness referred for pH monitoring. In 11 patients at least one pH parameter was abnormal and eight had an abnormal total AET. The group was very heterogeneous, however, including patients with previous tracheostomy and laryngeal carcinoma, and selection criteria were not stated. Wiener et al (1986b) were also the first to report the use of a pharyngo-oesophageal dual ambulatory pH probe in chronic hoarseness. Findings included the description of pharyngeal pseudo-reflux - a slow progressive fall in pH followed by an abrupt return to baseline which could be reproduced in volunteers during sleep by attaching the probe to the molars and may have been due to inherent properties of the equipment or of saliva. The phenomenon was observed in almost one quarter of patients. True pharyngeal reflux, on the other hand, was rare and only six episodes were detected in the 34 patients studied. Gaynor (1988) recorded reductions in pharyngeal pH in eight patients during a study of endotracheal intubation, and concluded that the altered level of consciousness of such patients might predispose to GOR, which might in turn contribute to the laryngeal complications of intubation. Katz et al (1988), reported pharyngeal reflux episodes in seven of nine patients with chronic dysphonia. Again, the group was heterogeneous and no selection criteria were stated. Furthermore, there was no control group and the extent of oesophagopharyngeal reflux in asymptomatic subjects remains unknown.

A variety of tests of oesophageal function were used by Ohman et al (1983) to investigate 58 patients with contact ulcer of the larynx. This is a rare condition described by Chevalier Jackson (1928) who attributed the erosion over the vocal processes of the true cords to voice abuse. Even in substantial series, only three to eight cases are recruited per annum (Peacher 1961, Brodnitz 1961, Ward et al 1980). Only 43 of Ohman's patients underwent oesophageal investigation and some abnormality of function was found in 74%. The findings were heterogeneous and dysfunction recorded if any one of a number of tests were positive - an approach open to error on statistical grounds, particularly as the tests were performed up to 10 years after diagnosis. The results of Ohman's study also failed to explain the reported success of voice therapy in contact ulcers and granulomas (Peacher 1961, Cooper and Nahum 1967). Vocal therapy is likely to have a considerable psychological content (Bloch and Gould 1974) and its success casts doubt, therefore, on the validity of previous uncontrolled trials of antacid therapy where the placebo component was not assessed.

Many questions remain unanswered about laryngeal symptoms and pathology in relation to GOR. The basic mechanism of laryngeal irritation - oesophagopharyngeal reflux - was originally demonstrated radiologically but studies attempting to record lowering of pharyngeal pH have encountered methodological problems, including pharyngeal pseudo-reflux and probe mobility, and have yielded conflicting results. Both the normal pharyngeal acid exposure and the relationship of UOS function to oesophagopharyngeal reflux remain unknown. Some studies attempting to correlate reflux with laryngeal symptoms have used inadequate methodology and have relied heavily on uncontrolled trials of antacid therapy, while others have reported highly selected small groups of patients with heterogeneous pathology. The precise diseases which might be caused or exacerbated by GOR are likewise unknown. Early interest centred on contact ulcer, but this is extremely rare compared with GOR and vocal abuse seems to be a more likely aetiological factor in the majority of patients. It is reasonable to suppose that any refluxed irritant material would principally affect the posterior larynx but the presence of pale, squamous epithelium in this region may be simply a normal variant. There is clearly a need for a substantial survey of laryngological patients to determine whether there is a pattern of symptoms, signs and histological findings which can be attributed to reflux.

3:3 CERVICAL DYSPHAGIA

'Several pints of saliva a day are swallowed without effort, a function that is best appreciated when it is missing. Hence the apparent salivary excess in Parkinsonism' - Edwards 1973.

Cervical dysphagia has a multiplicity of organic causes, several of which will not be considered here, eg foreign body impaction, extrinsic compression by goitres or cervical neoplasia and referred sensation from distal obstructive lesions. Present day interest in cervical dysphagia as an isolated symptom dates from the work of Brown Kelly (1919), Paterson (1919) and Vinson (1922), who were later associated eponymously with a condition of cervical dysphagia encountered principally in middle aged women. Brown Kelly found associations with anaemia, dyspepsia and neuroticism and described a mucosal stricture or web in the postcricoid region whose dilatation by the passage of an oesophagoscope effected greater symptomatic relief than simple bouginage. Like Paterson (1937), he considered that the female preponderance was not a reflection of neurosis in view of the established higher incidence of post-cricoid carcinoma in female patients compared with the excess of male patients with carcinoma of the lower oesophagus. Brown Kelly also distinguished the syndrome from hysteria by the absence of globus sensation and of intermittent symptoms, and proposed that it was due to cricopharyngeal spasm secondary to an imbalance of innervation - either sensory hyperaesthesia or excessive motor discharge. Rogers' (1935) subsequent report of bilateral cervical sympathectomy was based on the concept of the production of cricopharyngeal spasm by excessive sympathetic discharge, which was subsequently disproved by Lund (1965b). Although apparently successful in the single patient reported, the operation does not seem to have been pursued either by the author or by any other investigator.

Vinson (1922), on the other hand, considered that the negative radiological studies in his 69 subjects (57 female) implied a hysterical condition which could be distinguished from globus hystericus by the obstruction of food passage. Vinson believed that nutritional changes were secondary to this dysphagia. As in the cases of functional spasm described by Munro (1811) the symptom responded to bouginage. The absence of radiological abnormality, ie presence of a web, in Vinson's study may, however, have been due to the poor resolution of available methods (Section 2.3.1). Nonetheless, it is interesting that even a much later radiological study of 100 consecutive cases of dysphagia demonstrated no abnormality in 21% (Osborne et al 1960) and there is little doubt that so-called 'functional dysphagia' (Otell and Coe 1935) does exist, although its physiological basis remains unknown. Fiorella et al (1986) performed UOS manometry in patients with functional dysphagia or globus sensation. In some members of both groups there were abnormalities of UOS function, such as incomplete relaxation, which were attributed to psychological factors. Negus (1938) proposed that both iron deficiency anaemia and cervical dysphagia were due to 'hypopharyngitis' which could also progress to post-cricoid carcinoma. Evans (1930) thought that some cases might be caused by sero-negative chronic endosyphilis. Wynder and Fryer (1958) found iron deficiency anaemia related to geographic, nutritional and menstrual factors in a study of 150 patients (133 female) with Paterson Brown Kelly syndrome, of whom 47% were anaemic and 77% had a past history of dysphagia. Jacobs (1962) found iron deficiency anaemia in 31% of patients with postcricoid carcinoma and described pernicious anaemia in a small number. In a later study of 55 patients (3 with webs), almost half were noted to have deficient absorption of vitamin B_{12} and it was proposed that iron deficiency was secondary to the atrophic gastritis of pernicious anaemia (Jacobs and Kilpatrick 1964). In the same year, however, Elwood et al (1964) performed a unique epidemiological study of over 4000 subjects to ascertain the incidence of the 'only consistent' finding in the Paterson Brown Kelly syndrome - cervical dysphagia. A definite history of dysphagia localised between the hyoid bone and the suprasternal notch was obtained in 1% of males and 5% of females and 15% of those with dysphagia had evidence of upper oesophageal webs. There was little evidence that females with dysphagia, either alone or in association with a web, had iron deficiency. It was felt that previous studies on hospital-based patient populations may have over-emphasised the haematological associations, and that postcricoid dysphagia could best be regarded as a single symptom, in some cases associated with a web or stricture in the area. The absence of iron deficiency was in keeping with the demographic pattern of Plummer-Vinson syndrome, which was not recognised in Africa despite a high incidence of severe iron deficiency (Jacobs and Kilpatrick 1964). A later study by Seaman (1976) of 108 patients with webs found that, although 32 patients were anaemic, only five had associated dysphagia.

It appears likely, therefore, that in some females with cervical dysphagia, there is an associated iron and/or vitamin B_{12} deficiency but that the incidence of these findings depends on population selection. More severe cases may have a higher incidence, although the finding of a web is the exception rather than the rule. On direct enquiry, up to 60% of patients with globus pharyngis admit to some degree of dysphagia (Batch 1988) and the fact that the incidence not only of iron deficiency and neurosis but also of post-cricoid carcinoma is higher in females than in males, has contributed to the confusion. A functional aetiology in some patients, as originally proposed by Vinson (1922), cannot be excluded, although the concept of psychogenic cricopharyngeal spasm (Lindsay 1955) remains speculative. Paterson (1919) felt that upper oesophageal mucosal changes might exacerbate spasm but Edwards (1974) described spasm as a 'nebulous concept' and felt that most cases were attributable to mucosal changes which were unrelated to muscular function. Among such mucosal changes, heterotopic gastric mucosa has been described as a cause of cervical dysphagia (Raine 1983, Hamilton et al 1986b, Ollyo et al 1988), high stricture (Steadman 1988) and, rarely, adenocarcinoma (Carrie 1950). The 'inlet patch' was detected in 3.8% of 420 upper gastrointestinal endoscopies (Jabarri et al 1985) and in the majority of cases was not associated with specific symptoms.

One of the first causes of organic cervical dysphagia to be identified was the posterior median pulsion diverticulum between the thyro- and cricopharyngeus (Ludlow 1769). Although very rare, with even major centres seeing fewer than 30 cases per annum (Welsh and Payne 1973), the aetiology and treatment of pharyngeal diverticula have been extensively investigated. The consistency of the site of origin was repeatedly confirmed by anatomical studies (Halstead 1904, Keith 1910, Hill 1926) but the precise causes of herniation were unclear. Negus (1950) proposed a variety of predisposing conditions - hypopharyngitis, stricture, excessive contraction or lack of relaxation of the cricopharyngeus - although operations to remove diverticula under local anaesthesia revealed that small diverticula were actually pulled into the gullet at the moment of maximum UOS contraction (Hiebert 1976). The 3:1 male:female ratio remains unexplained (Nanson 1974) but it must be remembered that acquired lateral pharyngoceles also have a marked male preponderance.

Pedersen et al (1973), in an early manometric study, failed to show any difference in UOS tone or pharyngo-oesophageal motility between patients with diverticula and controls. In an uncontrolled study of six patients, on the other hand, Lichter (1978) claimed that premature UOS relaxation and contraction resulted in abnormally high pharyngeal pressure generation. Ellis and Crozier (1981) also found reduced UOS tone, and premature UOS relaxation and contraction in 10 patients undergoing cricopharyngeal myotomy for pharyngeal diverticula. Duranceau et al (1983b) found significantly lower UOS tonic pressures in 10 pharyngeal pouch patients than in age-matched controls and four patients showed varying degrees of pharyngo-oesophageal incoordination. The published tracings suggest, however, not only that UOS after-contraction was inadequately recorded but also that incoordination may have been defined imprecisely. Knuff et al (1982) had also found reduced UOS tonic pressure in nine pharyngeal pouch patients and proposed that this may have been a secondary phenomenon due to the presence of the pouch. A careful analysis of swallow timing failed to demonstrate incoordination of pharyngeal contraction with UOS relaxation.

Some of the conflict of manometric findings in pharyngeal diverticula can be attributed to the methodology of these early reports. Clinically, endoscopic or external division of the cricopharyngeus became an accepted treatment, either alone, or in combination with excision (Dohlman 1949, Dohlman and Mattsson 1960, Todd 1974, Welsh and Payne 1973, Zuckerbraun and Bahna 1979). The complication rate of pouch excision remains high in small series (Todd 1974), although it is apparently reduced where experience is extensive (Payne and King 1983). Many of the complications arise from creating an opening into the pharyngeal lumen (Girard 1896) and have led to a revival of diverticulopexy in place of diverticulectomy for medium-sized pouches, despite the theoretical risk of missing the rare complicating intradiverticular carcinoma (Wychulis et al 1969, Nanson 1976, Baraka and Sadek 1985).

Cricopharyngeal myotomy was first used in neurological dysphagia following bulbar poliomyelitis with apparently successful results (Kaplan 1957), a finding thought to be at variance with the first manometric recordings in patients with bulbar poliomyelitis, myaesthenia gravis and dystrophia myotonica (Kramer et al 1957), as it was shown that UOS tone and coordination were normal but that there was a primary pharyngeal weakness. It is possible, however, that reduction of a normal resting cricopharyngeal pressure might aid deglutition where pharyngeal contraction is deficient, and cricopharyngeal myotomy became an established method for the treatment of cervical dysphagia (Blakeley et al 1968, Calcaterra et al 1975, Van Bel 1982). Early studies were based on radiological criteria of UOS dysfunction (Lund 1968, (Helsper et al 1974, Mitchell and Armanini 1975) and manometric criteria for the procedure remained doubtful. Henderson and Marryyatt (1977) found no difference of UOS tone or relaxation between normal subjects, patients with GOR and patients with dysphagia secondary to GOR. Others showed poor correlation of clinical improvement with pre-operative manometric abnormality (Orringer 1980) or with post-operative manometric or radiological improvement (Hurwitz et al 1975), although the results were claimed to be good in 64% of patients with oropharyngeal dysphagia and poor in only 12% (Hurwitz and Duranceau 1978, David 1985). Ellis and Crozier (1981) found the procedure to be of no benefit in four patients with bulbar palsy. In their total series of 20 patients, a mean decrease in UOS pressure of 63% was recorded.

Some of the inconsistencies were attributed to the technical problems of UOS manometry (Orringer 1980) and others may have been due to the self-limiting nature of some forms of acute dysphagia in the absence of neurological disease (Munro 1811, Parrish 1968), or to the heterogeneous nature of neurological diseases affecting swallowing - arterial, neoplastic, infective, degenerative and demyelinating (Edwards 1973). Identification of suitable age-matched controls may also have been an area of difficulty as the incidence of neurological dysfunction in the hypopharynx in asymptomatic male subjects over the age of 65 may be as high as 38% (Palmer 1976). There is also anecdotal evidence that even in severe brain stem disease, speech therapy aimed at eating modification and prevention of aspiration can obviate the need for cricopharyngeal myotomy (Schultz et al 1979). Myotomy may have a specific role in patients with longstanding cervical dysphagia whose cricopharyngeus muscle undergoes fibrotic changes (Cruse et al 1979). A recent report of the use of a strain-gauge assembly in oculopharyngeal dystrophy (Fradet et al 1988) indicated that, although the only pre-operative abnormality was a poor pharyngeal contraction wave, the reduction in cricopharyngeal tone following cricopharyngeal myotomy was associated with a good clinical response.

The lack of manometric investigation in most recent reports of neurological dysphagia (Winstein 1983, Veis and Logemann 1985, David 1985, Gordon et al 1987, Price et al 1987, McIntosh et al 1987) may reflect a general disappointment in the value of the technique in the UOS and the greater availability of radiological investigation, but quantitative estimation of resting cricopharyngeal pressure is not possible by radiographic techniques (Kilman and Goyal 1976). Conversely, manometry may fail to detect failure of cricopharyngeal relaxation where the lumen is wider than the diameter of the manometric catheter, although still abnormally narrow. As manometric and manofluorometric methodology develops, there is clearly a need to reinvestigate functional and neurological causes of dysphagia to define more precisely the concomitant motor abnormalities, as many of the available reports were published before the radial asymmetry of the UOS had been documented and the low-compliance perfusion system or strain-gauge assemblies had been developed.

PART II: EXPERIMENTAL DATA

4. NORMAL PHARYNGO-OESOPHAGEAL MOTILITY

In 1983, the introduction of the micro-computer recording of pH data transformed the methodology of intraoesophageal pH monitoring (Pezzuoli et al 1983, Vitale et al 1983) as it soon became apparent that the analysis of digitised data was much more efficient and less subject to observer error than was the manual analysis of analogue tracings. Since that time, several groups have attempted to digitise the output of manometric chart plotters and to analyse the resultant data by computer (see Section 2.3.2). A further logical development is to perform the original manometric recording on a digitised computer system rather than on an analogue plotter. Such a recording method would be particularly suited to the study of pharyngo-oesophageal coordination in view of the many parameters to be studied for each swallow complex. A prototype computerised waveform analysis system was introduced in the early 1980s by Gaeltec Research Ltd (Skye, Scotland) using a Sirius computer. A later model, based on an IBM personal computer subsequently became available. The evaluation of this new recording system, whose software allows computerised calculation of wave amplitude and of time intervals, is described in the first two sections of this chapter.

It has also been known for several years that the critical limiting factor in the accurate measurement of pharyngeal pressure waves is the performance of the recording catheter. Orlowski et al (1982) showed by Fourier analysis of the frequency content of pharyngeal waves that recording accuracy up to 48 Hz was required for high-fidelity recording in the pharynx. The maximum rate of pressure change was also ten times greater in the pharynx (over 4000 mmHg/sec) than in the oesophagus, probably due to the functional characteristics of striated muscle. Both the frequency response characteristics and the post occlusion pressure rate rise of perfused catheters are, therefore, inadequate for pharyngeal recording. Siting of the pressure transducer within the catheter itself greatly increases the response rate as the only transducer delay is the transmisson of pressure across a light diaphragm. The use of perfused catheters with external transducers results in a delayed response due to the transmission of pressure through a column of fluid. Intraluminal strain gauges have a frequency response of over 1 KHz at a pressure of 100 mmHg, which is more than adequate for the recording of pharyngeal pressure waves whose frequency content requires recording accuracy up to 48 Hz. A comparison of a conventional perfused catheter with a catheter-mounted transducer assembly in the study of lower and upper oesophageal motility is described in the third section of this chapter.

The subsequent sections of Chapter 4 describe the use of a perfused sleeve sensor in the registration of tonic UOS pressure in a large number of healthy volunteers, and the effect of variables such as age, sex and bolus consistency on normal patterns of pharyngo-oesophageal motility.

4.1 DEVELOPMENT OF A COMPUTERISED MANOMETRIC WAVEFORM ANALYSIS SYSTEM

4.1.1 Recording Methods

The aim of the study was to compare the recording characteristics of a conventional chart recorder with those of a computer-based waveform analysis system. The chart plotter used was a 4-channel pen plotter (Elcomatic 750, Elcomatic, Glasgow) with a flat frequency response of 70 Hz $\pm$ 10% when attached to a direct current source.

The computer analysis system is based on an IBM personal computer (GR800, Gaeltec, Skye). The programme used during this study allowed a variable rate of pressure-sampling from 8 to 32/sec. A visual trace of manometric events is produced by the GR800 in up to six pressure recording channels and in a respiration channel. The pressures registered in each channel when an event marker is pressed during recording are listed after the tracing has been displayed. After recording, sections of the trace are selected by the operator for expansion. The operator selects a recording channel and the peak or average pressure in that channel over a chosen segment of display is computed. Time intervals in any channel can also be computed, correct to 0.01 sec. An automatic timing facility allows the cursor to sweep down from a selected peak in the top channel, giving peak-to-peak intervals in the five lower channels. A digital display of the selected peak and tonic pressures and of the time intervals may then be printed out with the displayed segment of tracing.

During the course of this and subsequent studies, several modifications to the programme were made at the suggestion of the author. These were incorporated into the software as the investigations proceeded. In all, six GR800 programmes were used at different stages of the studies reported in this chapter. These adaptations did not, however, affect the basic recording characteristics of the system. Modifications included the calculation of average (tonic) pressure instead of the area under the pressure curve and ultimately a data compression system was introduced. This allows a constant sampling rate of 32/sec but only those data points showing a change in pressure are stored in the memory. Where a pressure event occurs, the system samples it 32 times per second and stores these points, thus giving a high sample frequency without memory overload. Intragastric and intrapharyngeal zeroing of transducer tracings obviated the need to subtract mean intragastric or intrapharyngeal baseline pressures which was necessary in the early part of the study when the transducers were calibrated against atmospheric zero pressure. Transducer calibration was also modified to allow for the recording of occasional very high pressures encountered, particularly in the upper oesophageal studies. The original upper limit of calibration was 200 mmHg but this was altered to a displayed upper limit of 300 mmHg, with a linear extrapolation above this pressure. Numerous 'bugs' in the programme were also detected and rectified.

4.1.2 Study Protocol

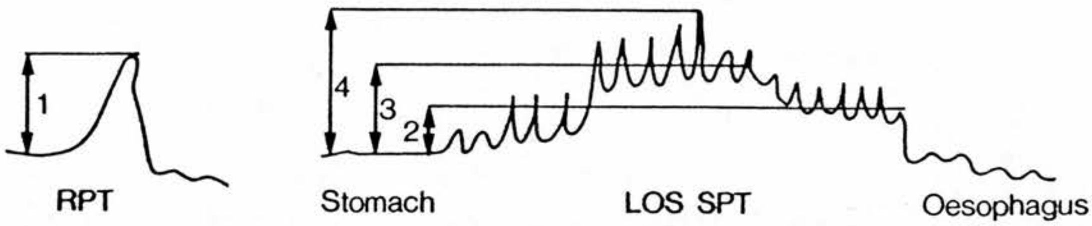
Manometric studies were performed using an Arndorfer ESM3 8-channel catheter, outer diameter 4.7 mm, perfused at 0.5 ml/min by a low compliance capillary hydraulic infusion pump and linked to each recorder by external transducers (Elcomatic 740). The initial manometric investigation in each patient was performed using the Elcomatic 750 chart recorder which was in routine clinical use at the time of the study. The entire procedure was then repeated under identical conditions with the GR800 recorder.

The catheter was passed transnasally until all sensors recorded intragastric pressure. Three rapid pull-throughs (RPTs) of the LOS were performed in full expiration. LOS mean RPT pressure (1 cm/sec) was calculated from three channels 1 cm apart at 90^{o} orientation. An LOS station pull-through (SPT) was then performed at 1 cm intervals. Mean mid-respiratory and peak inspiratory LOS pressure (Figure 4.1a, Nos 1, 2 and 4) were averaged from the same three channels. All LOS pressures were made relative to mean intragastric pressure. A series of 15 water swallows (5 ml bolus) at 20 sec intervals was then performed. Peristaltic amplitude was calculated from the last 10 swallows, 5 cm above the proximal margin of the LOS.

An SPT of the UOS at 0.5 cm intervals was performed using 2 channels 5 cm apart at 90^{o} orientation. For each channel the maximum tonic UOS pressure recorded during the SPT was calculated and the two values averaged to give maximum tonic UOS pressure (Figure 4.1b, Nos 3 and 4). The peak pressures in each channel following a dry swallow were also averaged to give peak UOS SPT pressure. A series of four 5 ml water swallows was then performed with one side-hole at the level of maximum tonic UOS pressure to record minimum UOS pressure on swallowing and peak wet swallow UOS after-contraction pressure. The duration of total UOS wet swallow complex was also noted. Peak wet swallow pharyngeal contraction amplitude was recorded 5 cm above this level (Figure 4.1c).

FIGURE 4.1 - LOS and UOS Manometric Parameters

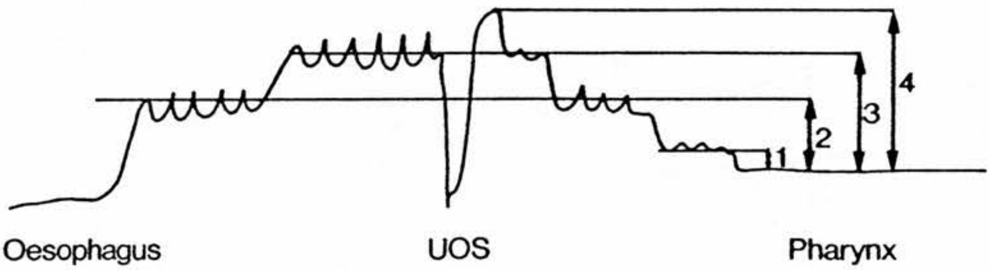
4.1a - LOS



1 = RPT pressure   2 = Mean tonic pressure

3 = Maximum tonic pressure   4. Peak inspiratory pressure

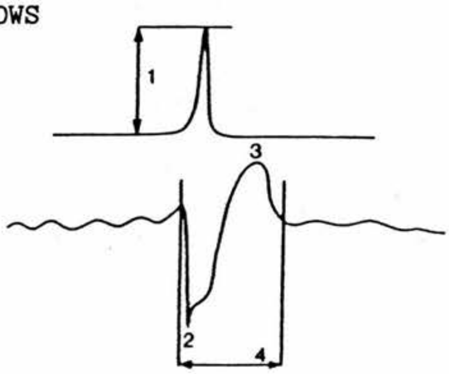
4.1b - UOS SPT



1 = Minimum tonic pressure   2 = Mean tonic pressure

3 = Maximum tonic pressure   4 = Peak pressure after dry swallow

4.1c - UOS WET SWALLOWS



1 = Pharyngeal pressure   2 = UOS minimum relaxation pressure

3 = UOS after-contraction   4 = Swallow duration

With the chart recorder, a paper speed of 2.5 mm/sec was used, increased to 25 mm/sec for UOS wet swallow studies. For UOS pressure measurements, intrapharyngeal pressure was taken as zero reference.

4.1.3 Subjects and Data Analysis

Thirty nine patients, 11 males and 28 females, aged 31 to 75 years (mean age 52 years) were studied. The patients had a variety of cervical symptoms, principally globus sensation (24 patients) and dysphonia (15 patients) and were undergoing oesophageal manometry in conjunction with intraoesophageal pH monitoring studies (see Section 5.3 and 6.3)).

Data analysis was by the SPSSX programme and included calculation of Pearson correlation coefficients (CR). These do not reflect differences in the magnitude of values when two investigative methods are compared (Bland and Altman 1986). To allow for the magnitude of the measured variable, a coefficient of repeatability was also derived for each parameter: CR = standard deviation of the mean difference divided by the average of the two mean initial values. The differences are likely to follow a Normal distribution because much of the intersubject variability has been removed. The CR is, therefore, a measure of variability which allows comparison of parameters whose mean values are different, eg different methods of tonic LOS pressure measurement. In this study it was also used to compare variability, including intrasubject variation, between the two recordings of different manometric parameters, eg LOS and UOS tonic pressures. The 95% confidence intervals (CI) of the mean difference between the two recording methods (Gardner and Altman 1986) were also calculated. CI = mean difference $\pm$ (t x SEM) where the t statistic is at the 5% level with the appropriate degrees of freedom (n-1 for sample size n). The 95% CI of the mean difference give an estimate of any bias of one recording method over another in the measurement of a given parameter. The significance of this bias was also evaluated by paired Student's t-test. The limits of agreement as defined by Bland and Altman (1986) were also calculated: these limits represent the range within which 95% of differences fall, ie mean difference $\pm$ 1.96 SD of the differences and are, therefore, an estimate of measurement error.

4.1.4 Results

The results of manometric study with the two recording methods are listed in Table 4.1. There was no significant sex difference in any parameter. Estimation of LOS length during SPT was the least closely correlated parameter ($r = 0.13$, NS) and the 95% CI of the mean difference indicate that LOS length was estimated to be up to 0.9 cm longer with the chart recorder (CR = 0.33). Estimates of UOS length with the two recorders were more closely correlated ($r = 0.50$, $p < 0.001$): the estimated length was a mean of 0.2 cm longer with the chart recorder (CR = 0.20, Table 4.1).

There was a good correlation of LOS pressure measurements with the two recording systems: for RPT pressure $r = 0.74$; for tonic SPT pressure $r = 0.61$; for peak SPT pressure $r = 0.58$ (all $p < 0.001$). Nonetheless, all three mean LOS pressures were higher when recorded with the chart recorder. The largest and most significant mean difference, observed with RPT measurements of the LOS (mean difference = 6.8 mmHg), is due in part to the greater magnitude of LOS pressure when recorded by the RPT method (see also Section 4.4.1). The coefficients of repeatability of LOS pressure measurements in the present study indicate that values differed by up to 42% (tonic SPT) between the two recording methods. The optimum repeatability was observed with peak LOS SPT pressure (CR = 0.33). The corresponding limits of agreement indicate the wide range of differences in SPT pressure between the two studies, eg for peak LOS SPT pressure, the limits of agreement were -28 to 40 mmHg. Although the two mean peristaltic amplitudes were almost identical (mean difference = 0.06 mmHg) the wide standard deviation of the differences in this

TABLE 4.1 - Comparison of Chart and GR800 Recordings (Arndorfer Catheter) in 39 Patients with Cervical Symptoms

(Pressures in mmHg)	CHART	GR800	MEAN DIFFERENCE[ø]	95% CI OF MEAN DIFFERENCE	PAIRED t	CR
LOS length (cm)	4.1	3.7	0.4	-0.07 to 0.9	1.72	0.33
RPT pressure	34	27	6.8	1.7 to 11.9	2.77*	0.40
SPT pressure - mean	17	14	2.4	0.2 to 4.6	2.18+	0.42
- peak	56	50	6.0	0.2 to 12.2	1.97	0.33
Peristaltic amplitude	88	88	-0.06	-11.4 to 1.3	-0.01	0.38
UOS SPT length (cm)	3.9	3.7	0.2	-0.05 to 0.5	1.74	0.20
maximum tonic	64	50	13.9	5.2 to 22.6	3.26**	0.43
peak	120	134	-14.3	-22.6 to -1.9	-2.34++	0.27
UOS wet swallow						
pharyngeal	68	58	9.7	0.9 to 18.5	2.24+	0.41
UOS minimum relaxation	-4	-2	-2.4	-5.0 to 0.2	-1.93	2.31
UOS peak after-contraction	125	129	-3.9	-21.3 to 13.4	-0.46	0.40
duration (secs)	3.4	4.8	-1.4	- 2.9 to 0.1	-2.39+	0.61

+ $p < 0.05$, ++ $p < 0.03$, * $p < 0.01$, ** $p < 0.005$

ø Difference = chart value - GR800 value measurement (CR = 0.38) imply a greater variability in peristaltic amplitude than in LOS peak pressure (limits of agreements -65 to 65 mmHg).

Tonic pressure measurements in the UOS were also higher if recorded with the chart recorder, and a greater degree of bias was observed than in the LOS (mean difference = 13.9 mmHg, 95% CI 5.2 to 22.6 mmHg, $t = 3.26$, $p < 0.005$). As in the LOS, this difference would have been obscured by reliance on correlation of the two values ($r = 0.70$, $p < 0.001$). Variability of tonic UOS pressure using the present protocol was greater than that of the least reproducible LOS parameter (CR = 0.43) and the limits of agreement were from -35 to 63 mmHg. Pharyngeal pressure was also significantly lower when recorded with the GR800 (mean difference = 9.7 mmHg). UOS peak pressures following both spontaneous dry swallows during SPT and 5 ml wet swallows were slightly higher with the GR800 although the bias was significant only for dry swallow after-contraction ($t = -2.34$, $p < 0.03$). The variability of peak UOS pressure following dry swallows was, however, less (SD of difference = 34 mmHg, CR = 0.28) than that of peak UOS pressure following wet swallows (SD of difference = 51 mmHg, CR = 0.41).

Mean UOS swallow complex duration was more than 1 sec shorter when recorded with the chart than with the GR800 and a further notable difference was in wet swallow minimum relaxation pressure which was usually recorded as being several mmHg lower with the chart recorder. An extremely wide range of differences was observed on repeat measurement (CR = 2.31, limits of agreement -16 to 11 mmHg).

4.1.5 Discussion

The present study constitutes a preliminary exploration of the recording properties of the GR800 recorder, and was undertaken during the early period of familiarisation with the recording equipment. Certain features of the study design are, therefore, likely to have influenced the results. In all patients, the first recording was made with the Elcomatic chart in order not to compromise the quality of manometric data available for clinical purposes. This may have concealed order of study differences. All records were analysed by a single observer (JAW), albeit in a random sequence because at this time other laboratory staff had not been trained in the analysis of UOS manometric tracings. This may have inadvertently introduced a bias to the findings. An unavoidable problem encountered was the nature of the analogue plotter available for comparison with the GR800. The Elcomatic 750 is a 10-year old pen recorder and has now been superseded by high fidelity jet or photosensitve polygraphs. Unfortunately, the high cost of such an instrument precluded its purchase for comparative studies. The tracings obtained with the Elcomatic 750 during studies of wet swallow pharyngo-oesophageal motility were of rather poor quality, with occasional disappearance of the trace during rapid pressure changes. More importantly, the study was performed prior to the investigation of the effect of intra-subject variability (see Section 4.4). This variability may have considerably influenced the estimation of certain parameters, eg tonic UOS pressure, which was recorded from only two side-holes at 90^{o} orientation. Because of the marked radial asymmetry of the UOS, minor alterations in catheter orientation during the study are likely to have contributed to the observed difference in UOS tonic pressure with the two recording methods used (CR = 0.43).

Nonetheless, the data from this preliminary study are reported because they yielded several useful pieces of information. Firstly, the suggestion by Bland and Altman (1986) that parametric (Pearson) correlation was an unsatisfactory statistical method for the comparision of two methods of measurements has been confirmed. The correlation coefficients for all parameters except LOS length and pharyngeal pressure were greater than 0.59 ($p < 0.001$) but this clearly underestimates the true variability of the measurements concerned (Table 4.1). The paired t-test offers some advantages over correlation, eg UOS dry swallow after-contraction, which had the highest correlation coefficient of any parameter studied ($r = 0.78$) was found to have a significant separation of mean values ($t = 2.34$, $p < 0.03$). This increase in measured pressure with the GR800 computer was a relatively consistent bias, however, as reflected in the low CR (0.27). On the other hand, the corresponding limits of agreement (-81 to 52 mmHg) are a better indicator of the true magnitude of the variability. It appears, therefore, that much lower CRs would have to be achieved for this measurement to be of use clinically. Similarly, mean peristaltic amplitude was almost identical with both recorders and this might have been attributed to an independence of radial asymmetry and perhaps also to the fact that for each subject the value was a mean figure of 10 wet swallows, but the CR of peristaltic amplitude (0.38) is seen to be among the highest observed. This is because, although the mean difference was less than 1 mmHg, the standard deviation of the differences was 33 mmHg. Thus the apparent consistency of measurement of mean peristaltic amplitude is due to the cancelling out of large increases in amplitude on repeat study in some subjects by the presence of large decreases in amplitude in others.

The use of a similar coefficient of repeatability to compare different measurements of LOS pressure as suggested by Welch and Drake (1980) is further considered in Section 4.4. The present preliminary results suggest that peak tonic LOS SPT pressure (CR = 0.33) may be a less variable measurement than either tonic SPT pressure (CR = 0.42) or mean pressure from three RPTs (CR = 0.40).

In this study, however, tonic SPT was defined as the mean pressure over the LOS length (Figure 4.1a, No 2). While this can be derived almost instantaneously from the GR800, on a chart tracing this pressure must be subject to considerable observer error.

Accordingly, it was decided in subsequent studies to record tonic LOS SPT pressure over the segment of maximum pressure, rather than over the whole length of the sphincter, although the problem of respiratory fluctuation in tonic lower and upper sphincter pressures remains (see Section 4.2). The present preliminary results show that all three LOS measurements were somewhat lower when recorded with the digitised GR800 recorder. The same trend was observed with pharyngeal and tonic UOS pressures but peak UOS pressures were, on average, slightly higher with the computer recorder.

During analysis of pharyngo-oesophageal motility, wet swallow duration appeared to be highly variable (CR = 0.61) and the standard deviation of wet swallow relaxation pressure (6.7 mmHg) was so high that there appeared to be little, if any, association between the chart and computer measurements (limits of agreement = -6 to 11 mmHg). The mean difference (-2.4 mmHg, 95% CI -5 to 0.2 mmHg) tends to suggest that there was a bias towards the recording of lower UOS minimum relaxation pressures with the chart recorder. There are two possible explanations. The first is that the sample rate of the GR800 recorder is inadequate to capture the moment of greatest UOS relaxation. More likely is the alternative explanation that the negative pressures (relative to intrapharyngeal pressure) of the chart recorder represent a form of 'overshoot artifact' caused by pen inertia during the first stage of relaxation. This latter explanation was supported by examination of the chart wet swallow patterns which showed a sharp downward flick at the onset of relaxation, followed by a more sustained relaxation at a pressure of several mmHg higher.

Some months after the completion of this pilot study, it became possible to perform simultaneous pressure measurements with both recording systems. This development allowed the problems of intrasubject variability, order of study differences and observer bias to be avoided and is described in Section 4.2.

4.2 VALIDATION OF COMPUTERISED RECORDING IN OESOPHAGEAL MANOMETRY

4.2.1 Methods

The aim of the study was to obtain simultaneous pressure recordings on an analogue plotter and on the GR800 computerised waveform analysis system. Both recorders are described in Section 4.1.1. An 8-channel analogue output module (Blue Chip Technology, Clwyd, Wales) was inserted into the GR800 mother board to allow digital to analogue conversion of the output signal. A cable link was established between the two recorders to allow instantaneous transmission of pressure data from the GR800 to the Elcomatic 750 recorder whose pressure scale was adjusted from the GR800 keyboard as necessary (range = 10 to 80 mmHg/cm).

A Gaeltec strain gauge assembly was used to overcome some of the methodological problems encountered in the previous study (Section 4.1.5). The catheter has an outer diameter of 2.8 mm and carries six strain gauges at 60^{o} orientation, three at one level at 120^{o} orientation. There is one sensor 3 cm above this level and two are at 3 cm and 8 cm below the three-sensor level. Two of the three-sensor level transducers were not used in the present study, however, as the Elcomatic 750 has only four available channels. The transducers are described here in some detail as the catheter was also used in several subsequent studies.

Each sensor is made from beryllium copper sheet with a sensing area chemically etched to the required thickness, surrounded by a thicker, supporting border. The use of a metal diaphragm, with diffused silicon chip gauges attached, allows significant reduction in transducer size and eliminates the potential electric shock hazard of silicon diaphragms (see Section 2.3.2). The metal diaphragm is coated on both sides with an insulating layer of silicon monoxide by vacuum evaporation. A pattern of two strain gauges and associated gold contacts are evaporated onto one side. The strain gauges are evaporated thin film chromium cermet, which has properties similar to metal and semiconductor. The two resistive gauges form two arms of a Wheatstone bridge which has its balancing network at the recorder end of the cable. Together with these passive resistors, there is temperature compensation, obtained by shunting and rebalancing the bridge over the required temperature range to achieve minimal zero shift. When tested in isolation, the metal diaphragm has a resonant frequency of up to 5 KHz (ie if struck, it will 'ring' at this frequency). The frequency response also depends, however, on the location of the sensor and once it has been fixed in the catheter, the frequency response is 1 to 3 KHz. Only above this frequency is the response of the system attenuated by the catheter. At a frequency response of 1000 cycles per second to a pressure of 100 mmHg, therefore, the maximum rate of rise is 100 mmHg in 0.00025 sec (ie 1/4000th sec) as each sine wave cycle has two component downstrokes and two component upstrokes. The rate of pressure rise (dP/dt) of the strain gauges far exceeds that of any biological pressure change: the registration of a rise of 1000 mmHg between two data points at a sample rate of 64/sec is typical, ie the dP/dt is over 60,000 mmHg/sec when the sensor is tapped. This precludes any meaningful bench comparison of strain gauges with conventional perfused side-hole or diaphragm catheters whose dP/dt is a hundred times smaller.

4.2.2 Study Protocol

The strain gauge transducers were calibrated in air and the assembly passed transnasally until all the sensors were within the stomach, where they were zeroed to mean intragastric pressure during quiet respiration. Simultaneous pressure recordings from the four selected sensors were made on the GR800 and Elcomatic recorders. The orientation of the sensors was anterior, posterior and left and right anterior. In view of the poor quality tracings with the chart recorder previously obtained during UOS wet swallow studies (which required a paper speed of 25 mm/sec) these were excluded from the present investigation. A paper speed of 100 mm/min was used for tonic pressure measurements, increased to 2.5 mm/sec for oesophageal body studies.

An RPT at 1 cm/sec of the LOS in full expiration was recorded in all four channels. An SPT of the LOS at 1 cm intervals was then performed. Maximum tonic mid-respiratory pressure and peak inspiratory pressure were recorded in the three uppermost sensors (Figure 4.1a, Page 90, Nos 3 and 4). With the lowermost sensor in the LOS, a series of 10 water swallows (5 ml bolus) was performed and mean distal peristaltic amplitude and duration derived. The sensors were then withdrawn into the pharynx and zeroed relative to intrapharyngeal zero reference. Three RPTs of the UOS at 1 cm/sec during quiet respiration were performed and the mean pressure for each RPT calculated from the three uppermost sensors. (The lowermost (tip) sensor could not be used for UOS pressure recording in all subjects: in those with a high sphincter the catheter had been virtually removed before this sensor was within the high pressure zone). Finally, a timed SPT of the UOS at 0.5 cm intervals with 20 sec at each station was performed. Maximum tonic and peak (post dry swallow) UOS pressure (Figure 4.1b, Page 90, Nos 3 and 4) in each of the three uppermost sensors were recorded.

Finally, a bench comparison was made of the two recorders. The Gaeltec catheter was placed in a sealed chamber and a known pressure applied from a sphygomanometer. Pressure was increased to a pressure of 50 mmHg and recorded in each of the four channels of the two recorders simultaneously. The procedure was repeated ten times, giving a total of 40 measurements for each recorder.

4.2.3 <u>Subjects and Data Analysis</u>

The combined recordings were obtained from the first 21 consecutive patients attending for manometric investigation following the installation of the GR800 analogue board. These comprised eight males and 13 females, aged 20 to 82 (mean = 56) years. The patients included 10 with globus sensation, seven with cervical dysphagia (two of neurological origin), three with atypical chest or throat pain and one patient studied following laryngeal radiotherapy. Full details of manometric findings in these conditions are given in Chapter 6 and Chapter 7.

The aim of the study was to assess the comparability of the two recording methods used, and was not concerned with inter-observer variation in analysis of manometric data. Accordingly, the GR800 tracing was displayed and analysed segmentally. The sections corresponding to those analysed by the GR800 were then indicated on the chart tracing. The marked sections of chart data were later analysed independently by Mrs Anne Pryde, who was not aware of the GR800 results. Both sets of data were then entered into an SPSSX file for analysis. Comparison of means was performed by both Student's t-test and by the Wilcoxon matched-pairs signed-rank test. Non-parametric (Spearman) correlation coefficients (r_s) and Pearson correlation coefficients (r) were computed. The 95% CI of the mean difference, the coefficients of repeatability and the limits of agreement between the two recorders were calculated as described in Section 4.1.3. As both parametric and non-parametric correlation and a comparison of means gave very similar results, only the non-parametric analysis will be reported. In this and in subsequent studies the z statistic of the Wilcoxon rank sum and Mann Whitney U-test is quoted: this is the W or U statistic corrected for ties. For the bench comparison data, the limits of agreement for each recorder with the known applied pressure (50 mmHg) were derived from the mean and SD of the differences of the 40 recorded pressures.

4.2.4 Results

Results of the 14 manometric parameters studied are listed in Table 4.2. The mean differences between the two measurements are much lower than those listed in Table 4.1, with a corresponding

TABLE 4.2 - Results of Simultaneous Analogue and Digitised Manometric Recording in 21 Subjects

(Pressures in mmHg)	GR800	CHART	MEAN DIFF$^{\phi}$	95% CI OF MEAN DIFF	Z	LIMITS OF AGREEMENT	CR
LOS - RPT (n = 14)	27	29	-1.3	-2.6 to -0.07	-1.89	-5.5 to 2.8	0.08
SPT tonic pressure	16	19	-3.3	-4.0 to -2.5	-4.0**	-6.4 to -0.1	0.09
SPT peak pressure	45	46	-0.8	-1.8 to 0.2	-2.54+	-5.3 to 3.5	0.05
Peristalsis - amplitude	55	58	-3.1	-5.0 to -1.1	-3.06++	-11.7 to 5.6	0.08
duration (secs)	2.82	2.88	-0.06	-0.3 to 0.2	-0.82	-1.0 to 0.9	0.16
UOS mean RPT pressure - 1	46	47	-1.4.	-1.8 to -1.1	-3.92**	-3.0 to 0.16	0.02
2	51	52	-1.1	-1.5 to -0.6	-3.66++	-2.9 to 0.75	0.02
3	46	47	-1.2	-1.8 to 0.7	-3.36**	-3.4 to 0.91	0.02
UOS tonic SPT pressure - L ant	27	29	-2.0	-3.2 to 0.8	-2.61++	-7.3 to 3.3	0.09
ant	37	41	-4.4	-5.8 to -3.0	-3.84**	-10.5 to 1.7	0.08
post	65	71	-5.9	-8.4 to -3.4	-3.82**	-16.3 to 4.5	0.08
UOS peak SPT pressure - L ant	60	59	0.7	-0.3 to 1.6	-1.21	-3.5 to 4.8	0.04
ant	68	68	-0.06	-1.6 to 0.5	-1.26	-4.8 to 3.7	0.03
post	85	84	0.8	-0.4 to 2.0	-1.08	-4.2 to 5.8	0.03

+ $p < 0.05$, ++ $p < 0.01$, * $p < 0.001$, ** $p < 0.0001$ - Wilcoxon matched-pairs signed-rank test.

ϕ Difference = GR800 value - chart value reduction in the 95% CI of the mean difference. Spearman correlation coefficients approached unity for many pressure measurements and, with the exception of peristaltic duration (r_s = 0.42,NS), were all greater than or equal to 0.95 ($p < 0.001$). With the same exception, the coefficients of repeatability indicate a measurement error of less than 10% for all pressures. As in the preliminary comparison (Section 4.1), there was a bias such that GR800 pressure measurements were slightly lower than those obtained with the chart recorder. This bias accounts for the significant differences shown by the Wilcoxon signed-rank test for all pressures, with the exception of UOS peak SPT pressure following dry swallows (Table 4.2).

The limits of agreement indicate that 95% of pressure differences lie within 10 mmHg of the mean difference. Plots of the difference between the methods against the average recorded measurement are shown in Figure 4.2a and 4.2b and allow investigation of any possible association of measurement error and the true value. The latter remains unknown, and the average of the two measurements is the best estimate available. For none of the parameters is there a systematic variation in measurement over the range of differences, ie the magnitude of the bias is independent of the magnitude of the measured pressure. The figures also illustrate the approximation of most of the mean differences to zero. The clearest bias to lower recordings with the GR800 is seen with LOS SPT tonic pressure measurement.

The results of the bench test of the two recorders showed that for the GR800 recorder, the mean difference of the 40 applied pressures was 1.6 mmHg (SD = 1.7 mmHg) and the limits of agreement were -1.8 to 4.9 mmHg. For the chart recorder, the mean difference was 2.0 mmHg (SD = 2.3 mmHg) and the limits of agreement were -2.5 to 6.5 mmHg,

FIGURE 4.2a -

Plots of Difference Against Mean of GR800 and Chart Pressures I

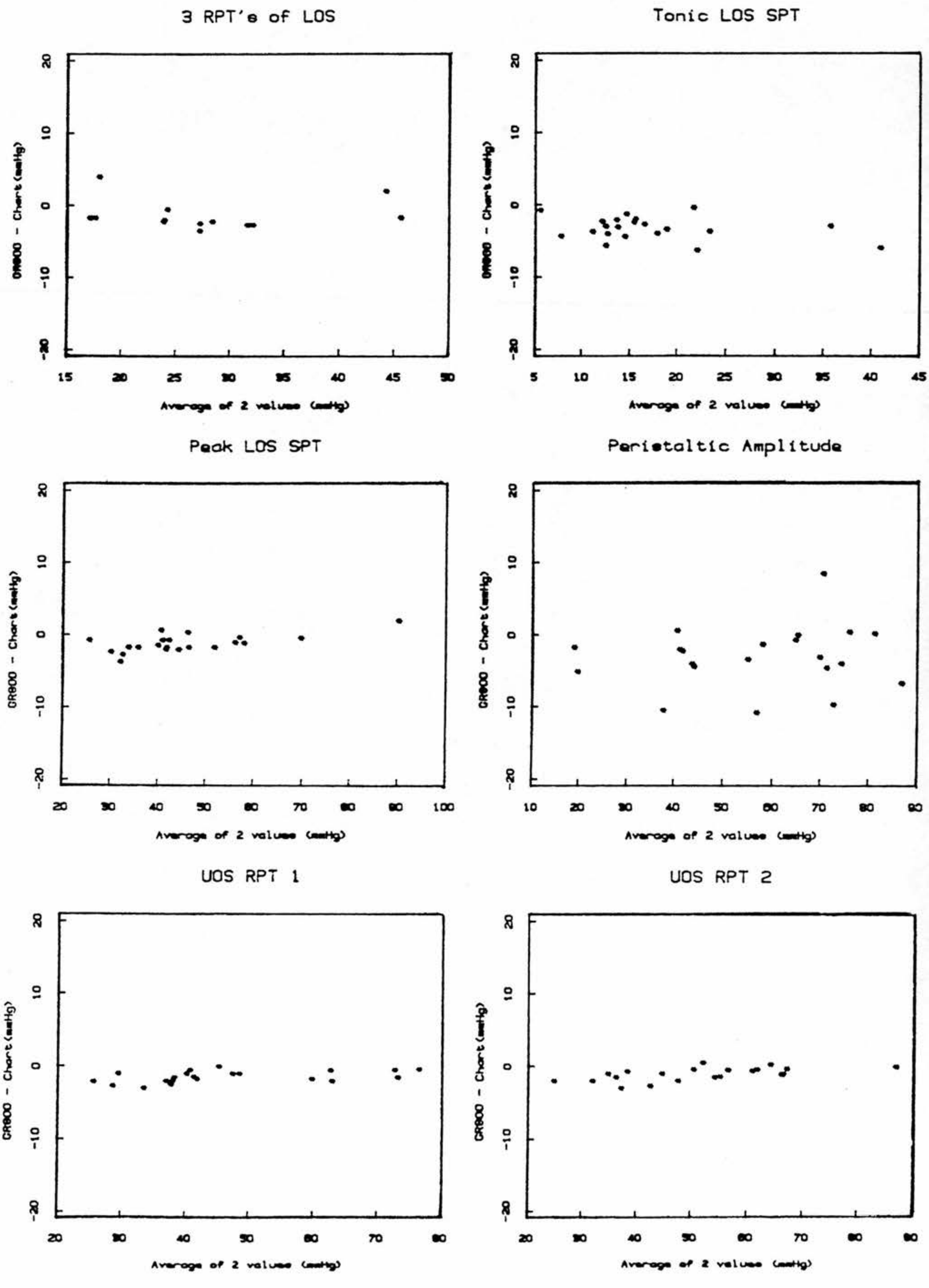
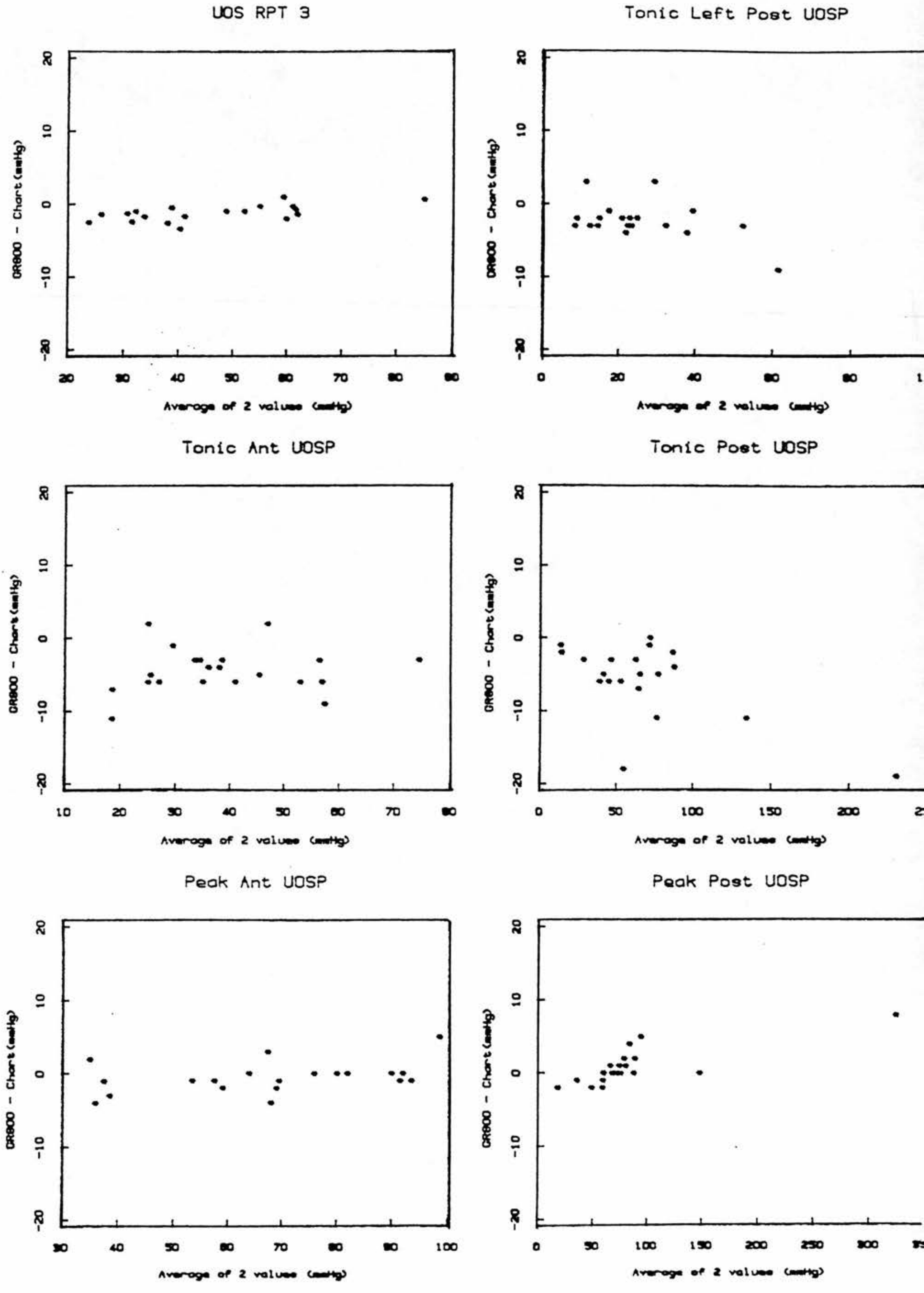


FIGURE 4.2b -

Plots of Difference Against Mean of GR800 and Chart Pressures II



4.2.5 Discussion

The use of simultaneous digitised and analogue manometric recording has not previously been described. The results of this study show a high degree of comparability of pressure measurements in the lower and upper oesophagus between a conventional chart recorder and a computerised waveform analysis system when the problem of biological variability is eliminated by signal-splitting and possible rotational variation is reduced by increased circumferential sampling. Mean pressures recorded with the GR800 computer were up to 5.9 mmHg lower (posterior tonic UOS pressure) than those of the chart recorder, although for most pressures the mean difference was less than 4 mmHg. Much of this difference may be due to differences in the recording characteristics of the two systems. There was a slight bias towards the recording of pressures a few mmHg greater than the applied pressure of 50 mmHg by both recorders but the bias was slightly greater with the chart recorder (limits of agreement = -2.5 to 6.5 mmHg) than with the GR800 recorder, which also showed a narrower range of differences (limits of agreement = -1.8 to 4.9 mmHg).

Other factors are also likely to make minor contributions to the observed differences. Firstly, the pen tracing clearly has a perceptible width and when recording a pressure 'peak' it is usual to note the very uppermost part of this line. In practice this would account for no more than 1 mmHg difference on the present scale of 10 mmHg/cm. Secondly, the precise calculation of mean tonic sphincter pressures is not possible by manual analysis of chart recordings even when only the segment of maximum tonic pressure (Figure 4.1c, Page 90) is considered as in the present study. The inspiratory phase of respiration is shorter than the expiratory phase and so the selection of a mid-respiratory plane is likely to over-estimate sphincter pressure as the peaks above the midrespiratory plane are of shorter duration than those below the plane. While an experienced observer can allow for this, there remains an inevitable error in manual calculation of mean tonic sphincter pressure which explains the greater variability of tonic SPT pressures and RPT pressures in both the upper and lower sphincters (see CRs, Table 4.2). A third potential source of error is the assessment of baseline reference pressure. With the GR800 recorder, once intragastric or intrapharyngeal zero reference has been established, baseline drift is negligible: intrapharyngeal zero reference is routinely checked on catheter withdrawal and has been found to be very consistent. The digital data output is, therefore, relative to either intragastric or intrapharyngeal pressure. The analogue output module used in the present study provides an identical baseline on the manometric trace, but during manual analysis, the baseline must be extrapolated by the observer. The greatest variability observed was in peristaltic duration (CR = 0.16). It is felt that much of this is due to observer differences rather than to recording variables, as the precise moment of onset of peristaltic wave can be difficult to determine.

In summary, the analysis of simultaneous analogue and digital tracings by two independent observers has shown very close agreement in the two recording methods. There was, however, a bias to the recording of pressures of a few mmHg greater with the chart recorder. Are these differences of physiological significance? There are many persisting methodological differences in manometric interpretation. Precise criteria for diagnostic classification of manometric abnormalities remain controversial and the optimum methods of measuring even a simple peristaltic wave have yet to be standarised (G Vantrappen, personal communication 1988). Each laboratory must, therefore, establish its own normal ranges for manometric studies and differences of a few mmHg in observed pressures are unlikely to be of practical importance. The GR800 analysis system costs less than an equivalent high-fidelity chart recorder and was marginally more accurate than the Elcomatic 750 recorder on bench testing in the present study. The system reduces observer bias and both produces a digital output of pressures and time intervals and displays a six-channel manometric trace. With the advent of computerised diagnosis of lower and mid-oesophageal motility, the system also represents a logical advance in manometic technology. The future incorporation of a data base to the software will allow continuous accumulation of subjects' data which will greatly facilitate the investigation of different disorders. The results of the present study demonstrate that the GR800 waveform analysis system provides accurate registration of upper and lower oesophageal motility measurements.

4.3 COMPARISON OF ARNDORFER AND GAELTEC CATHETERS IN UPPER OESOPHAGEAL MANOMETRY

As already discussed (Section 2.3.2) there have been several reports suggesting that despite the development of low compliance capillary infusion pumps (Arndorfer et al 1977), the perfused catheters which are now used almost universally in the study of LOS and oesophageal body motility are unsuitable for the study of pharyngo-oesophageal motility (Dodds et al 1976, Orlowski et al 1982). The vented perfusate and the broad diameter of the catheter act as irritants and the frequency response and pressure rate rise are inadequate for pharyngeal recording. It is perhaps surprising that although miniature intraluminal strain gauges have been available for almost 40 years, there have been so few reported comparisons of the performance of these transducers with that of conventional perfused catheters in upper oesophageal manometry (Dodds et al 1975, Kaye et al 1977). The aim of the present study was to compare an intraluminal strain gauge assembly with an Arndorfer catheter in manometric study of both the lower and the upper segments of the oesophagus.

4.3.1 <u>Methods</u>

The two catheters compared in this study were the Arndorfer ESM3 and the 6-sensor Gaeltec intraluminal strain gauge assembly (Section 4.2.1) both linked to the GR800 computer recorder. Subjects were studied alternately with either the Arndorfer followed immediately by the Gaeltec catheter, or vice versa, to allow for order of study differences. The Arndorfer catheter protocol was as described in Section 4.1.2 but with the recording of minimum tonic UOS pressure in addition to maximum tonic and peak UOS SPT pressures (Figure 4.1b, Page 90, Nos 1, 3 and 4). An identical procedure was followed with the Gaeltec catheter but with the following differences in radial pressure sampling.

(a) Mean LOS RPT and LOS SPT maximum tonic mid-respiratory and peak inspiratory pressures (Figure 4.1a, Page 90, Nos 1, 3 and 4) were averaged from all six Gaeltec sensors (at 60^{o} orientation). Arndorfer catheter LOS pressures were recorded from three side-holes at 90^{o} orientation.

(b) UOS SPT pressures were averaged from six of the Gaeltec sensors (or five where the UOS was sited proximally) but from only two side-holes at 90^{o} with the Arndorfer catheter.

(c) During wet swallow studies of the UOS, the 3-sensor level of the Gaeltec catheter was sited at the level of maximum tonic UOS pressure and pharyngeal recordings made from the sensor sited 3 cm proximally in the pharynx. With the Arndorfer catheter, only one side-hole could be positioned in the UOS and pharyngeal pressures were recorded 5 cm above this level, ie 2 cm proximal to the Gaeltec recordings.

4.3.2 Subjects and Data Analysis

The study was performed in 23 patients, 9 males and 14 females, aged 33 to 81 years (mean = 53 years). The patients were unselected consecutive attenders for upper oesophageal manometry, with principal complaints of globus sensation (14 patients) or dysphonia (9 patients). Data were analysed by the SPSSX programme by Spearman correlation coefficients (r_s) and Wilcoxon matched-pairs signed rank test. The 95% CI of the mean difference and coefficients of repeatability (Section 4.1.3) were also calculated. Order of study differences were assessed by paired Student's t-test.

4.3.4 Results

Results are listed in Table 4.3. The three mean LOS pressures were a few mmHg lower when recorded by the Gaeltec catheter (NS on Wilcoxon rank-sum test). The least reproducible LOS parameter was mean RPT pressure (CR = 0.42). Mean tonic LOS SPT pressure

TABLE 4.3 - Comparison of Arndorfer and Gaeltec Catheters in 23 Patients with Cervical Symptoms

(Pressures in mmHg)	ARNDORFER MEAN	GAELTEC MEAN	MEAN DIFF[ø]	95% CI OF MEAN DIFF	Z	CR
LOS length (cm)	3.8	3.2	0.6	0.16 to 1.09	2.18+	0.25
RPT pressure	28	26	2.1	-3.06 to 7.2	0.77	0.42
SPT pressure - mean	16	14	1.3	-1.4 to 4.1	1.01	0.39
- peak	44	40	4.2	-3.5 to 11.8	1.37	0.35
Peristaltic amplitude	89	77	12.3	-6.4 to 31.0	0.86	0.48
UOS SPT length (cm)	4.2	3.1	1.0	0.3 to 1.8	2.48+	0.40
maximum tonic	54	35	19.3	5.4 to 33.2	2.61*	0.67
minimum tonic	11	14	-2.8	-6.5 to 1.0	1.59	0.54
peak	116	118	-1.6	-23.9 to 20.7	0.26	0.41
UOS wet swallow						
pharyngeal pressure	68	108	-40.1	-76.3 to -3.8	2.16+	0.82
UOS minimum relaxation	-3	-2	-1.1	-3.6 to 1.3	1.0	2.46
UOS peak after-contraction	117	112	4.6	-28.8 to 38.0	0.04	0.60
Duration (secs)	3.35	3.05	0.30	-0.51 to 1.10	0.71	0.49

[ø] Mean difference = Arndorfer value - Gaeltec value; + $P < 0.05$, * $P < 0.01$, Wilcoxon signed-ranks was only 1.3 mmHg lower with the Gaeltec catheter (95% CI = -1.4 to 4.1 mmHg CR = 0.39) but the most reproducible parameter was LOS SPT peak pressure (CR = 0.35). All three LOS pressures showed significant correlation of Arndorfer and Gaeltec recordings on non-parametric correlation (r_s = 0.56, $p < 0.01$ RPT; r_s = 0.74, $p < 0.001$ tonic SPT; r_s = 0.53, $p < 0.03$ peak SPT). Peristaltic amplitude was somewhat less reproducible (mean difference = 12.3 mmHg, CR = 0.48, r_s = 0.40, NS) although, as with LOS tonic pressure measurements, the difference was not significant. Length measurements of both the LOS and the UOS were significantly shorter with the Gaeltec catheter.

Only two pressure measurements showed a significant difference on non-parametric testing between the two recording catheters. Mean maximum tonic UOS pressure was significantly lower when recorded by the Gaeltec catheter (CR = 0.67) and mean pharyngeal contraction was significantly greater with this catheter (mean difference = 40 mmHg). The most reproducible UOS wet swallow parameter was peak after-contraction (CR = 0.41). Duration of UOS wet swallow complex was on average 0.3 sec shorter when recorded with the Gaeltec catheter (95% CI -0.51 to 1.1 sec, CR = 0.49). Neither UOS SPT nor wet swallow parameters showed significant correlation (r_s = 0.14 to 0.32), with the exception of relaxation pressure (r_s = 0.66, $p < 0.002$).

The order of study with the two catheters made no significant difference on paired t-test to any parameter except Arndorfer catheter UOS relaxation pressure which was lower when that catheter was used first (mean = -4.9 mmHg) than when the Gaeltec catheter was used first (mean = -0.8 mmHg, t = 2.58, $p < 0.02$).

4.3.5 Discussion

The results show that LOS tonic pressures, peristaltic amplitude and maximum tonic UOS pressure were lower when recorded by the Gaeltec catheter, but the difference was significant only for tonic UOS pressure. It is known that pressures measured in the oesophagus increase as a function of catheter diameter (Biancani et al 1973, Kaye and Showalter 1974). The Arndorfer catheter used in the present study has an outer diameter of 4.7 mm, ie 1.9 mm greater than the Gaeltec catheter. A previous report of the effects of a comparable increase in diameter of a perfused catheter (Lydon et al 1975) showed significant increases in LOS tone and even greater increases peristaltic amplitude in the striated muscle oesophagus. Much the greatest absolute increase with increasing catheter diameter in Lydon's study was observed in UOS pressure, although the differences were wide-ranging, as in the present study (mean difference = 19.3 mmHg, SD of differences = 29.6). Some of the variation observed is almost certainly due to the 1.9 mm greater diameter of the Arndorfer catheter.

The generally poor repeatability of results in this study may, in part, explain why there are so few published reports of the comparison of different catheters. The wide variability (reflected in the very high CRs, Table 4.3) is a function both of catheter differences and of intrasubject variability which is likely to have been underestimated in reports of six to ten subjects (Kaye and Showalter 1974, Dodds et al 1975, Lydon et al 1975). A crude estimate of the contribution of intrasubject variability to the present results can be made by comparing the CRs in Table 4.3 with those of Table 4.8 (Section 4.4, Page 136) which indicate the intrasubject variability during repeat manometric study of 15 healthy subjects with the Gaeltec catheter. Although the CRs are not directly comparable, particularly as the repeat studies in Section 4.4 were performed at a mean interval of 12 weeks, rather than sequentially as in the present study, it appears that intrasubject variation is of the order of 30 to 40% for most LOS and UOS parameters (and greater than this for LOS RPT or wet swallow pharyngeal contraction amplitudes). This implies that most of the variation observed when two manometric catheters are compared in the LOS or oesophageal body is of biological rather than methodological origin and that catheter differences accounted for around 15% of the variation at these sites. In the UOS, however, maximum tonic pressure measurements (CR = 0.67) were clearly more variable than could be attributed to biological variation (CR of repeat study with Gaeltec catheter = 0.21, Table 4.8), although peak UOS SPT pressure was much less variable with the use of different catheters (CR = 0.41, Table 4.3). Similarly, while significant rank correlation of the two readings was observed for LOS pressure (and UOS wet swallow relaxation pressure), the two measurements of all other parameters of upper oesophageal motility failed to show a statistically significant association. The results support the suggestion that tonic UOS pressure is more sensitive than tonic LOS pressure to increasing catheter diameter, a finding which has been attributed to the different length/tension characteristics of smooth and striated muscle (Lydon et al 1975).

Another important difference between the two catheters used was that UOS pressure was recorded from only two side-holes at 90^{o} orientation with the Arndorfer catheter and from five or six sensors at 60^{o} orientation with the Gaeltec catheter. Despite minor differences in catheter orientation during a series of manometric studies, some of the greater magnitude of UOS pressure with the Arndorfer catheter is likely to be due to the orientation of the two Arndorfer channels studied. The differences in UOS length and minimum recorded tonic pressure between the two systems may also have been due to differences in radial sampling. The diameter of the Arndorfer catheter and the orientation of the side-holes appear to have influenced peak after-contraction pressures following dry swallows during UOS SPT by a much smaller amount, in contrast to the report of seven subjects by Dodds et al (1975) who found similar after-contraction pressures with their strain gauge assembly (112 mmHg) but much lower pressures with their perfused catheter (27 mmHg). The sole order of study difference observed (in Arndorfer catheter relaxation pressure) may well have represented a statistical artifact due to the large number of parameters being compared. Given the greater comparability of the two recordings in the LOS and oesophageal body, the narrow diameter of the Gaeltec catheter and its greater uniformity of radial sampling, the strain gauge assembly used in this study is likely to have given a more accurate estimate of UOS tonic pressure under physiological conditions than the perfused catheter.

Much the greatest difference between the two recording catheters was noted in pharyngeal contraction amplitude (CR = 0.82, Table 4.3). The 95% CI of the mean difference show that mean pharyngeal amplitude during a series of four wet swallows was between 4 and 76 mmHg greater with the Gaeltec catheter. This supports previous findings that the rapid frequency response of intraluminal strain gauges is necessary for the accurate recording of pharyngeal transients (Dodds et al 1972b, 1975 and 1976, Orlowski et al 1982). The design of the catheters available for evaluation in the present study resulted, however, in pharyngeal contraction recording at a level 2 cm lower in the pharynx with the strain gauge assembly. Orlowski et al (1982) demonstrated that mean pharyngeal pressure 1 cm above the UOS was 67% greater than that 6 cm above the UOS and it is also possible, therefore, that the more distal pharyngeal pressures studied by the Gaeltec catheter were of truly greater amplitude than those 2 cm higher recorded by the Arndorfer catheter. Pharyngeal contraction also shows a considerable intrasubject variation (Table 4.8, CR = 0.53). Also, although mean peak UOS after-contraction during wet swallows was very similar in the two studies, the results and their differences were very widely distributed (CR = 0.60). It is possible, therefore, that reliable estimates of mean pharyngeal and UOS contraction amplitudes require the study of a much larger number of water swallows in each subject.

In summary, it has been shown that a fine-bore strain gauge assembly which allows circumferential pressure measurement performs very much as a conventional perfused catheter in the LOS and oesophageal body although the strain gauge assembly records mean pressures 8 to 10% lower in the LOS and 14% lower in the distal oesophagus. Peak UOS contractions after dry swallows were very similar to those of the chart recorder. As a result of differences in diameter and in sensor orientation, there is a much greater difference between the two catheters in the recording of maximum tonic UOS pressure. Gaeltec catheter pressures were around 36% lower and are more likely to represent the true barrier of the upper high pressure zone in view of the known radial asymmetry of the UOS and the greater tension response to stretch of striated muscle. The 58% increase in mean pharyngeal contraction amplitude recorded with the Gaeltec catheter provides further support for the suitability of this type of strain gauge assembly in the study of pharyngo-oesophageal motility.

4.4 COMPARISON OF A SLEEVE CATHETER AND A STRAIN GAUGE ASSEMBLY IN 50 ASYMPTOMATIC VOLUNTEERS

4.4.1 Recording Methods and Study Protocol

Subjects were studied with two catheters, a modified sleeve catheter (Dent, Australia) and a catheter-mounted transducer assembly (Section 4.2.1) both linked to the GR800 recording system (Section 4.1.1). The sleeve catheter incorporates a 6 cm long sleeve sensor, D-shaped in cross-section, measuring 7.2 x 3.2 mm. Pressures were recorded from the sleeve sensor and from four side-holes, two at the upper and lower limits of the sleeve and two at 4 cm above and below the sleeve. All channels were perfused at 0.5 ml/min by a low compliance pneumohydraulic capillary infusion pump and linked by external transducers (Elcomatic 740) to the GR800 recorder. The sleeve sensor was orientated posteriorly in the UOS and catheter orientation confirmed on withdrawal. The side-holes were radially orientated with respect to the sleeve so that one was in the anterior plane, one right lateral and one each in the right and left posterolateral planes. The total radial pressure-sampling of the catheter was, therefore, 225^{o} and excluded the left anterior segment.

All subjects were studied in a recumbent position after a four hour fast. The catheters were used alternately so that half of the subjects were first studied with the sleeve catheter while the first study in the remainder was with the Gaeltec catheter. Respiration was recorded with a belt pneumograph.

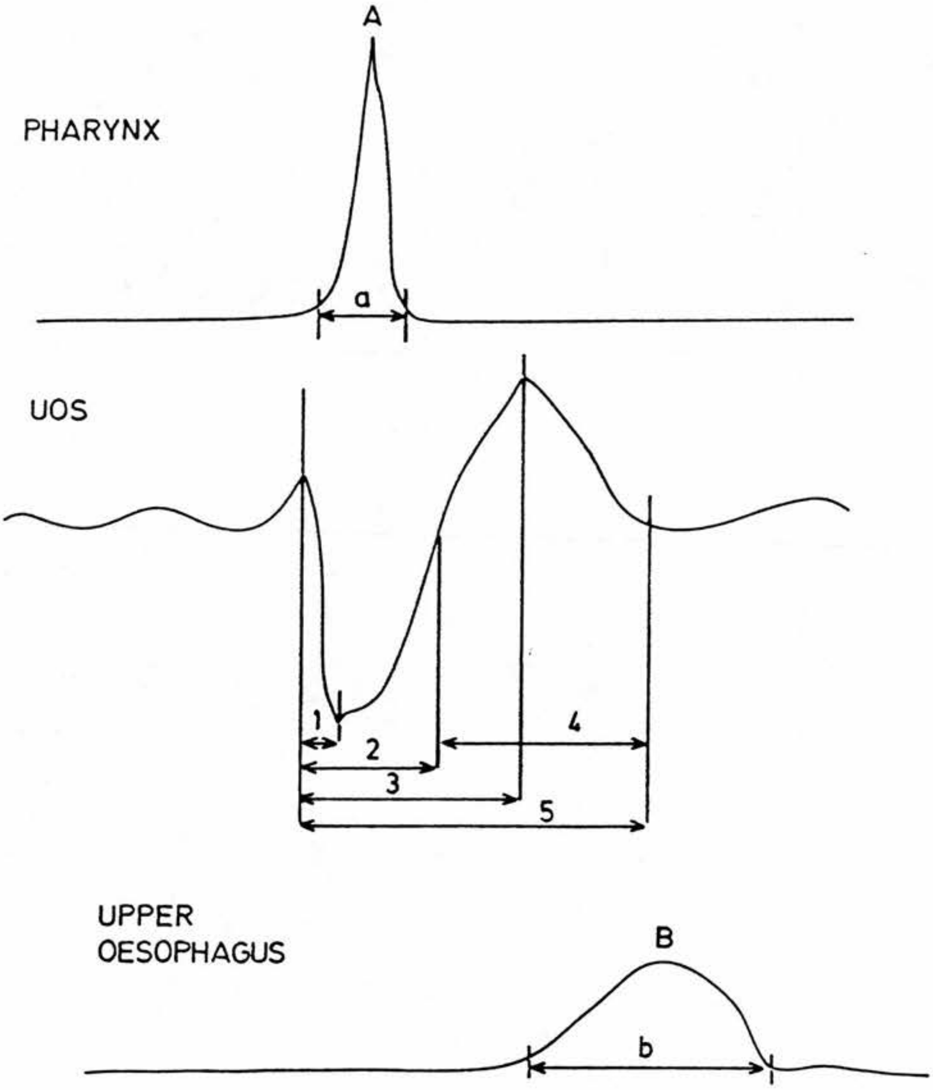
The Gaeltec catheter was used to measure LOS and oesophageal body motility. Three RPTs of the LOS in end-expiration at 1 cm/sec were followed by an SPT at 1 cm intervals. Mean end-expiratory RPT pressure, mean maximum mid-respiratory tonic SPT pressure and peak inspiratory SPT pressure (Figure 4.1a, Page 90, Nos 1, 3 and 4) were averaged from the six radially-disposed sensors. Peristaltic amplitude was recorded 5 cm proximal to the manometrically determined upper margin of the LOS in the first 35 subjects studied. In the remaining 15 subjects, the tip sensor was placed at the site of maximum tonic LOS pressure to allow simultaneous recording of LOS relaxation patterns. Peristaltic amplitude in this group was, therefore, recorded some 3 cm more proximally than in the initial 35 subjects. A series of 10 water swallows (5 ml bolus) at 20 sec intervals was performed. LOS and oesophageal body pressures were measured relative to mean intragastric pressure.

With each of the two catheters, an SPT of the UOS was performed at 0.5 cm intervals and maximum mid-respiratory tonic pressure and peak SPT pressure (following a dry swallow) measured (Figure 4.1b, Page 90, Nos 3 and 4). With the Gaeltec catheter, these were averaged from six sensors, or only five in some subjects whose UOS was sited more proximally. The catheter was passed with the consistent orientation of one channel posteriorly. UOS pressures with the sleeve catheter were recorded a) from the posteriorly orientated sleeve sensor and b) from the average of the four adjacent side-holes.

Following the SPT of the UOS, a series of four 5 ml water swallows was performed to assess pharyngo-oesophageal coordination. For this part of the study, the Gaeltec catheter was positioned with the three-sensor level at the site of previously determined maximum tonic UOS pressure. UOS minimum relaxation pressure and peak after-contraction pressure were averaged from the three sensors. Pharyngeal contraction was recorded 3 cm proximally (Figure 4.1c, Page 90, Nos 1 to 3). The sleeve catheter was sited with the proximal part of the sleeve sensor and the side-hole at its upper end at the level of maximum tonic UOS pressure, and pharyngeal pressure was recorded 4 cm proximally.

The parameters of pharyngo-oesophageal motility measured in this and subsequent studies are illustrated in Figure 4.3. In the present study, whose principal aim was to compare two recording

FIGURE 4.3 - Temporal Parameters of Pharyngo-oesophageal Motility



AB	=	pharyngo-oesophageal wave velocity
a	=	duration of pharyngeal contraction
b	=	duration of upper oesophageal contraction
1	=	time to minimum UOS relaxation
2	=	duration UOS relaxation
3	=	time to peak UOS after-contraction
4	=	duration UOS after-contraction
5	=	UOS swallow complex duration

catheters, the time intervals measured were time from onset of swallow to minimum relaxation, peak after-contraction and the end of the swallow complex (Figure 4.3, Nos 1, 3 and 5). All pressures were recorded with intrapharyngeal pressure as zero reference. The entire investigation was repeated in 15 subjects, 11 males and four females, at 8 to 15 weeks' (mean 12 weeks') interval.

4.4.2 Subjects and Data Analysis

Fifty healthy volunteer subjects, 28 males and 22 females, aged 17 to 62 years (mean = 33; SD = 11 years) were recruited. No subject had any history of globus, dysphagia, chest pain, antacid therapy or significant present or past medical history likely to influence results. Four subjects experienced heartburn more than once per month and 24 were cigarette smokers. The subjects comprised hospital medical, nursing and paramedical staff and volunteers recruited through a newspaper advertisement. I am most grateful to all these individuals for their cheerful cooperation with the study.

A total of 88 variables for each subject was analysed by the SPSSX programme. Paired Student's t-test and Spearman correlation coefficients (r_s) were used to compare the results of different methods of recording LOS pressure and the Gaeltec and sleeve catheter results, which were shown by frequency histograms to have an appropriately Normal distribution. The 95% CI of means and of mean differences and the coefficients of repeatability were calculated as described in Section 4.1.3. The chi-square test with Yates' correction was used in the assessment of axial asymmetry. Repeat studies (in 15 subjects) were analysed by Wilcoxon matched-pairs signed-ranks test.

4.4.3 Results - LOS and Oesophageal Body

Principal results are listed in Table 4.4a. Although measured at end-expiration, mean RPT pressure was significantly greater than tonic mid-respiratory SPT pressure ($t = 2.5$, $p < 0.02$). The 95% CI of mean tonic SPT pressure (14 to 18 mmHg) are slightly closer than those of mean RPT pressure (15 to 21 mmHg), a reflection of the smaller standard error and SD of tonic SPT measurements. The peak inspiratory pressure is clearly much the highest LOS pressure parameter (mean = 34 mmHg, 95% CI 30 to 38 mmHg). The SD of the mean difference between RPT and SPT pressure was 6.9 mmHg (CR = 0.42). Although the magnitude of LOS pressure varied significantly according to the method of measurement, there was a good correlation of the three LOS parameters: $r_s = 0.63$ RPT/tonic SPT; $r_s = 0.61$ RPT/ peak SPT; $r_s = 0.71$ peak/tonic SPT (all $p < 0.001$).

Analysis of LOS radial asymmetry (Table 4.4b) shows that all pressures recorded from the right posterior strain gauge were significantly lower on paired t-test than those of the other five channels. (Peak SPT pressures were not recorded from the right anterior channel in all subjects). Maximum LOS pressures were observed in the left or posterior quadrants. This finding was also present in a group of patients with cervical symptoms in whom LOS asymmetry was assessed by RPT (n = 24), and by tonic (n = 48) and peak (n = 31) pressure measurements (Table 4.4b). Paired t-test comparison showed that all right posterior LOS pressures in the total group were significantly lower than the mean pressure or the pressure from any channel (all $p < 0.001$). The combined data from the total group of 98 patients and controls is illustrated schematically in Figure 4.4 which demonstrates clearly the lower pressures recorded on both RPT and SPT from the right posterior quadrant of the LOS. The mean LOS length on SPT was 3.4 cm (SD = 1.0).

Mean LOS minimum relaxation pressure (2 mmHg) was recorded in the right anterior (tip) sensor whose tonic LOS pressure recording was

TABLE 4.4a - LOS and Oesophageal Body Motility in 50 Healthy Volunteers Recorded with a Strain Gauge Assembly

(Pressures in mmHg)	X	SD	RANGE
LOS - mean RPT pressure	18	9	7 - 51
- tonic SPT pressure	16	7	3 - 35
- peak SPT pressure	34	13	13 - 80
- wet swallow relaxation pressure+	2	4	-7 - 5
Peristalsis - amplitude	87	37	23 - 226
- velocity (cm/sec)+	3.1	0.7	2.3 - 4.4
Time from onset LOS relaxation			
- to minumum relaxation (sec)+	5.0	1.35	1.73 - 6.68
- to end relaxation (sec)+	10.74	1.90	8.35 - 14.33

+ calculated in 15 subjects.

TABLE 4.4b - LOS Radial Asymmetry in Volunteers and Patients

(Pressures in mmHg)	CONTROLS			PATIENTS		
		SPT			SPT	
ORIENTATION	3 RPTs	MEAN	PEAK	3 RPTs	MEAN	PEAK
Posterior	18	20	40	25	16	41
Left posterior	19	18	41	26	15	45
Left anterior	24	18	39	28	18	51
Anterior	17	13	28	19	12	35
Right anterior	17	16	--	20	--	--
Right posterior	13**	9**	24*	16+	9**	26++
MEAN	18	16	34	22	14	39

+ P < 0.001 vs Mean and two Left channels

++ p < 0.001 vs all except Posterior channel (p < 0.01)

* p < 0.001 vs all except Anterior channel (p < 0.05)

** p < 0.001 vs all

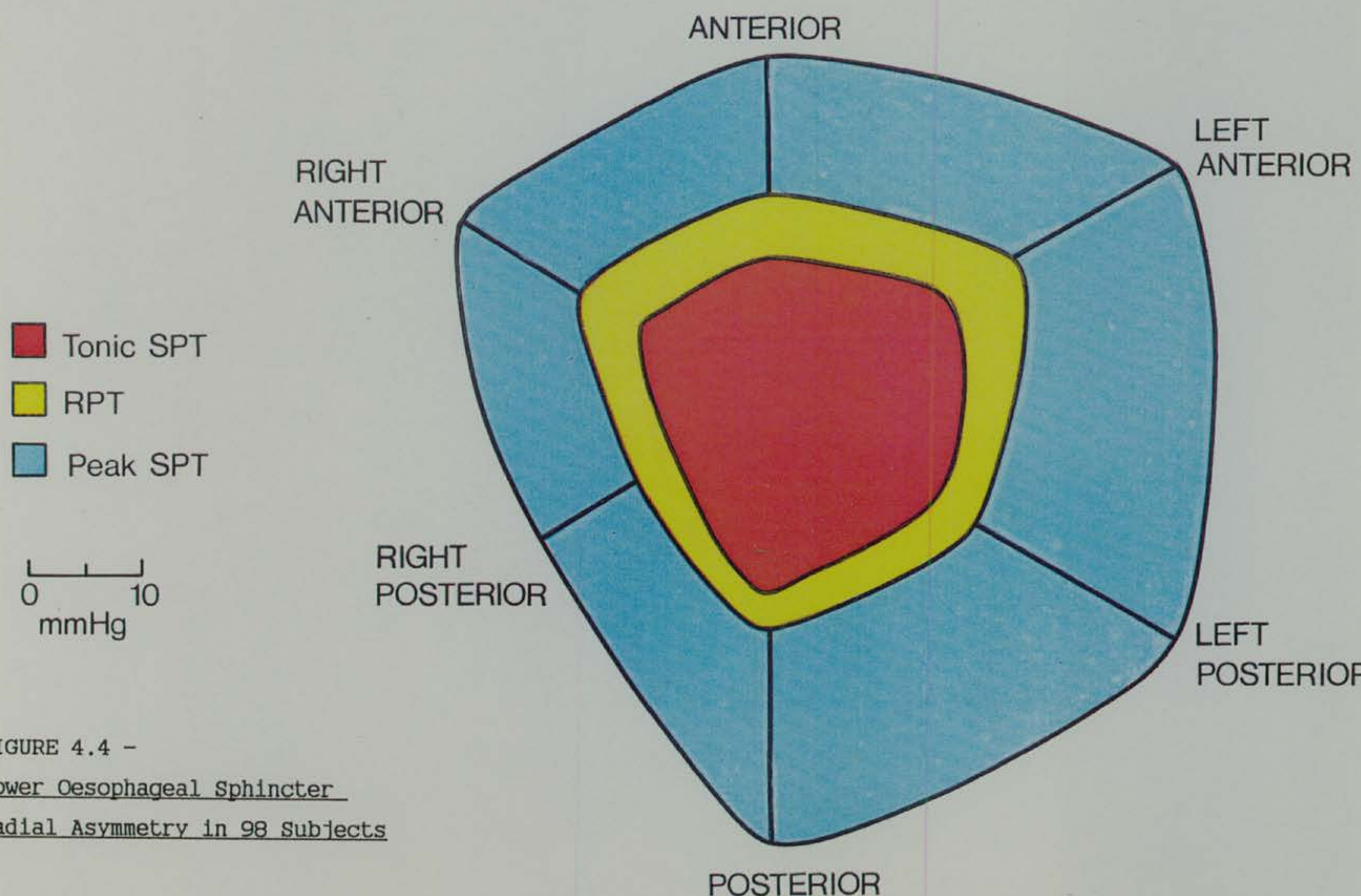


FIGURE 4.4 -

Lower Oesophageal Sphincter

Radial Asymmetry in 98 Subjects

16.2 mmHg, ie there was a mean reduction of 87% in LOS tone during wet swallows. A wide range of normal peristaltic amplitude was observed (Table 4.4a) and the peristaltic pressures were independent of LOS pressure. In this series there was no relationship of peristaltic amplitude with age (r_s -0.10) and there was also no significant difference on an unpaired t-test between the 35 subjects aged 35 years or less (mean = 88 mmHg) and the 15 subjects aged over 35 years (mean = 83 mmHg). There was no significant sex difference in any LOS or peristaltic parameter, nor between the 25 subjects studied first with the Gaeltec catheter and those studied first with the sleeve catheter. LOS pressures were 1 to 3 mmHg higher in smokers and mean peristaltic amplitude 13 mmHg lower (NS).

4.4.4 Results - UOS Station Pull-Through

Results of UOS SPT with the Gaeltec and sleeve catheters are listed in Tables 4.5a, 4.5b and 4.5c. Mean sleeve sensor measurements, which were recorded from the posterior plane, were significantly higher than either mean side-hole or Gaeltec catheter pressures. The mean pressures recorded from five or six of the Gaeltec catheter strain gauges were also significantly lower than those recorded from the four sleeve side-holes. These differences are illustrated in Figure 4.5. The greatest mean difference (44 mmHg) was observed between Gaeltec catheter and sleeve sensor pressure measurements. The sleeve sensor maximum tonic pressures were also much more widely distributed than the mean (circumferential) maximum tonic UOS pressures recorded with the Gaeltec catheter as shown in Figure 4.6. As with previous comparisons between different recording systems (Tables 4.1, 4.2 and 4.3) there was less variability among peak SPT pressures (CR = 0.22 to 0.33) than among maximum tonic pressure measurements (CR = 0.40 to 0.42). The correlation among the three systems for each of the two SPT pressures was highly significant ($p < 0.001$ for all r_s coefficients), yet the differences in magnitude of the measured pressures were equally significant

TABLE 4.5 - Manometric Findings on UOS Station Pull-Through with Gaeltec and Sleeve Catheters in 50 Healthy Volunteers

4.5a - Sleeve Sensor vs Average of 5 or 6 Gaeltec Strain Gauges

UOS PRESSURE (mmHg)	SLEEVE SENSOR MEAN	SLEEVE SENSOR SD	GAELTEC MEAN	GAELTEC SD	MEAN DIFF	95% CI OF MEAN DIFF	t*	r_s*	CR
Maximum tonic	83	32	40	15	44	36 to 52	11.6	0.66	0.42
Peak (dry swallow)	126	41	96	31	30	20 to 40	5.6	0.52	0.33

4.5b - Sleeve Sensor vs Average of 4 Side-Holes

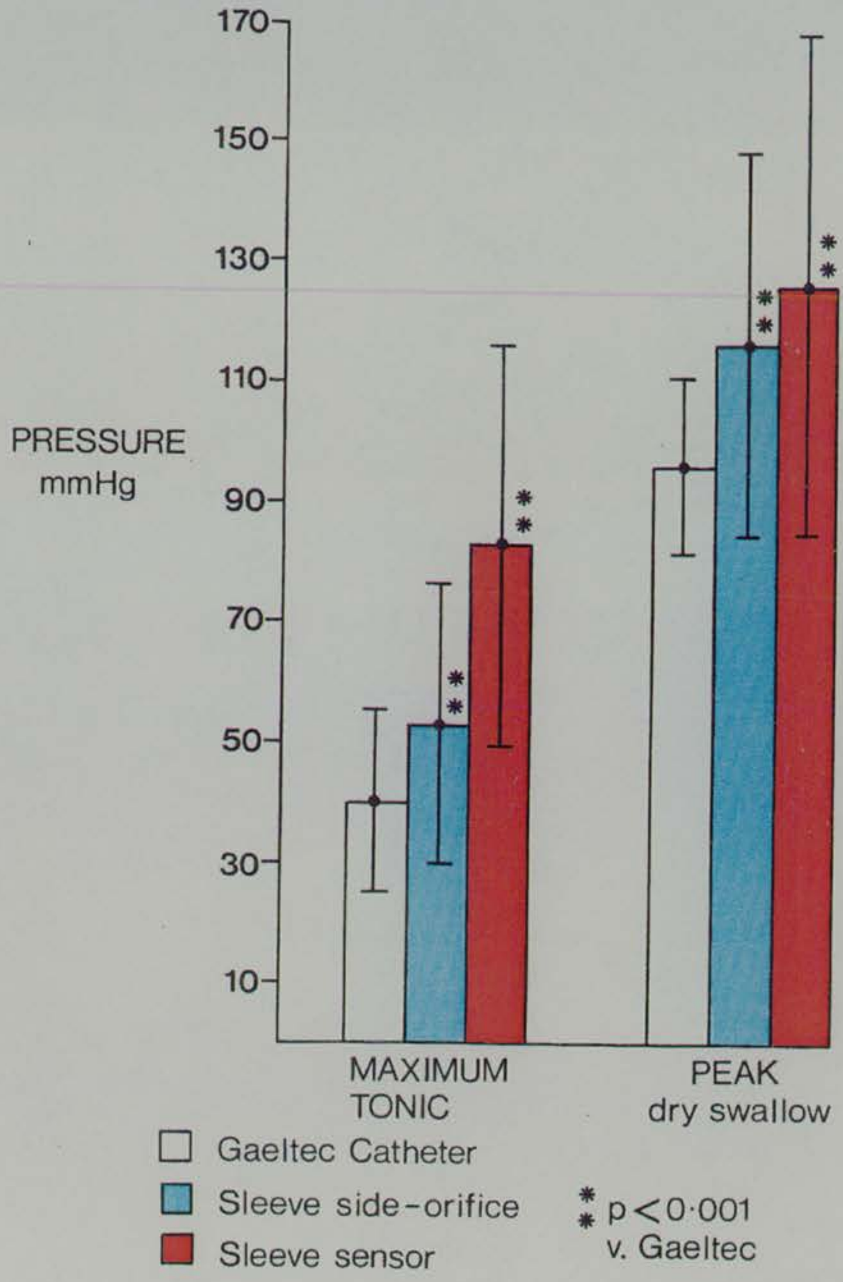
UOS PRESSURE (mmHg)	SLEEVE SENSOR MEAN	SLEEVE SENSOR SD	SIDE-HOLE MEAN	SIDE-HOLE SD	MEAN DIFF	95% CI OF MEAN DIFF	t*	r_s*	CR
Maximum tonic	83	32	53	23	31	23 to 39	7.8	0.62	0.41
Peak (dry swallow)	126	41	115	32	11	3 to 19	2.9	0.81	0.22

4.5c - Average of 4 Side-Holes vs Average of 5 or 6 Gaeltec Strain Gauges

UOS PRESSURE (mmHg)	SIDE-HOLE MEAN	SIDE-HOLE SD	GAELTEC MEAN	GAELTEC SD	MEAN DIFF	95% CI OF MEAN DIFF	t*	r_s*	CR
Maximum tonic	53	23	40	15	13	8 to 18	5.0	0.42	0.40
Peak (dry swallow)	115	32	96	31	19	9 to 28	3.9	0.56	0.32

* $p < 0.001$ for all tests

FIGURE 4.5 - Comparison of Mean Upper Oesophageal Sphincter SPT Pressures Recorded from 5 or 6 Gaeltec Strain Gauges, 4 Perfused Sleeve Catheter Side-holes and the Sleeve Sensor (SDs are indicated)



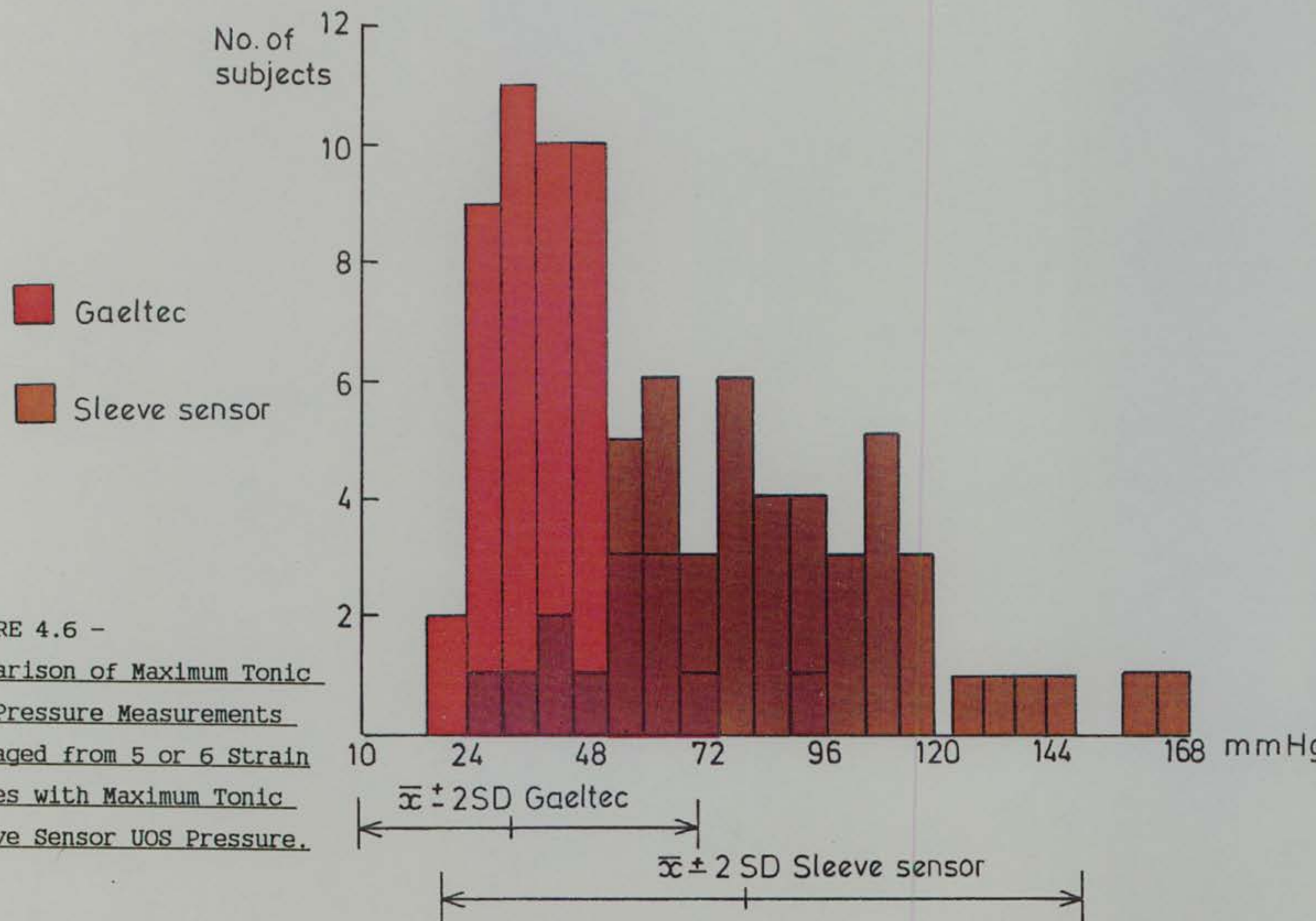


FIGURE 4.6 – Comparison of Maximum Tonic UOS Pressure Measurements Averaged from 5 or 6 Strain Gauges with Maximum Tonic Sleeve Sensor UOS Pressure.

TABLE 4.6a - Radial Asymmetry of UOS Station Pull-Through in 50 Healthy Volunteers (pressures in mmHg)

ORIENTATION	GAELTEC TONIC MIN	GAELTEC TONIC MAX	GAELTEC PEAK	SLEEVE TONIC MIN	SLEEVE TONIC MAX	SLEEVE PEAK
Posterior	21ø	67**	140*	60+	83	126
Left posterior	19	40	113	13	37	88
left				13	31	79
Left anterior	13	28	77			
anterior	19	42	91	20	102++	189++
Right anterior	16	26	68			
Right posterior	14	25	79	16	44	102
MEAN+	17	40	96	15	53	115

+ Sleeve catheter means are 4 side-holes

ø $p = 0.02$ vs mean, $p < 0.001$ vs 2 right and left ant channels

* $p < 0.001$ vs mean and all Gaeltec channels except left post ($p < 0.02$)

** $p < 0.001$ vs mean and all other Gaeltec channels

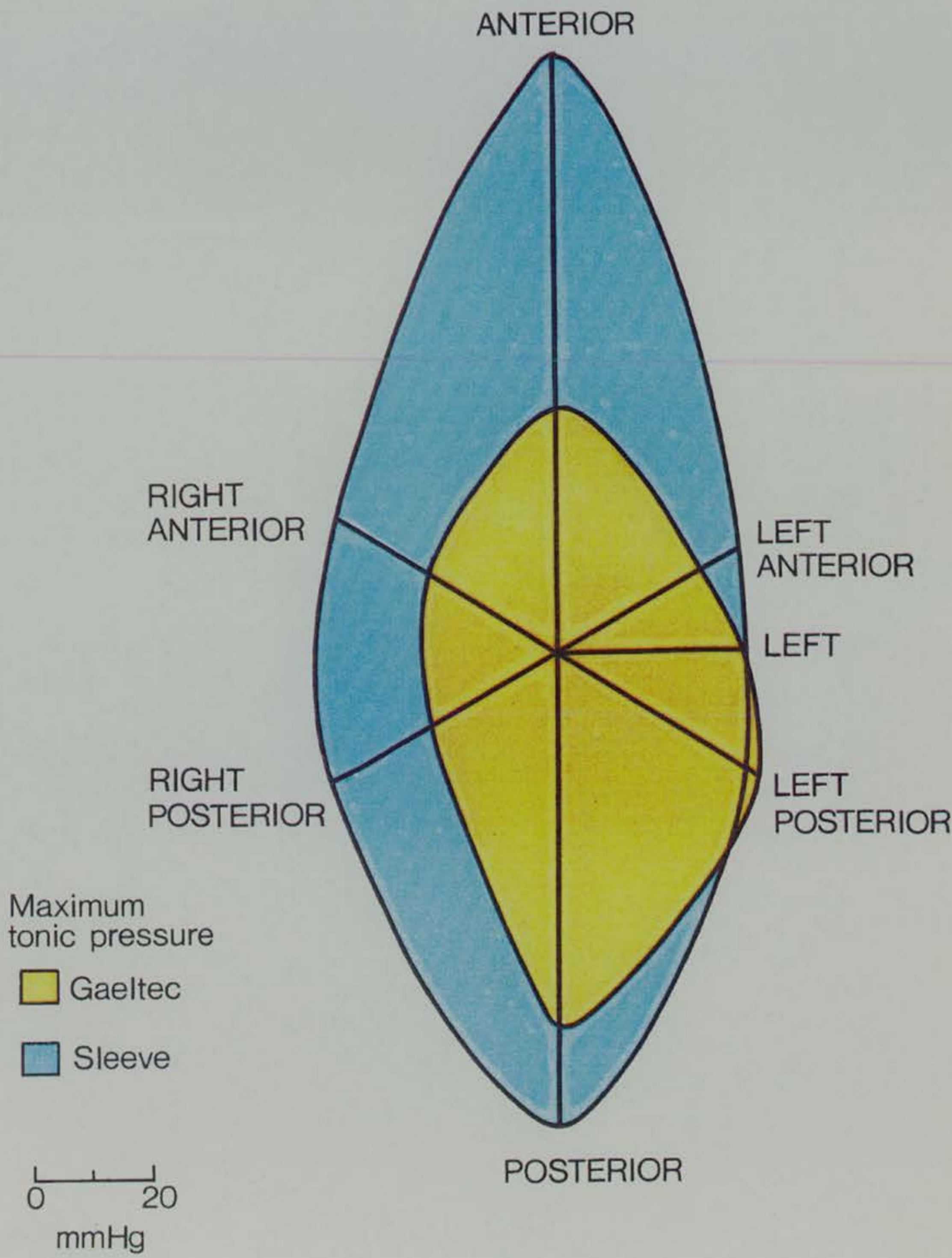
+ $p < 0.001$ vs all other minimum tonic pressures

++ $p < 0.001$ vs all other peak pressures

TABLE 4.6b - Axial Location of the Anterior and Posterior Zones of Maximum Tonic Pressure in 49 Healthy Volunteers

	MALES	FEMALES	TOTAL
Anterior - Distal	2	2	4
Central	6	13	19
Proximal	20	6	26
Posterior - Distal	15	7	22
Central	9	14	23
Proximal	4	0	4

FIGURE 4.7 - Upper Oesophageal Sphincter Radial Asymmetry Recorded by the Gaeltec and Sleeve Catheters in 50 Healthy Volunteers



($p < 0.001$ for all t statistics).

The UOS SPT pressures recorded from single transducers were compared to assess radial asymmetry (Table 4.6a) and the radial distribution of mean maximum tonic pressures in the 50 volunteers is illustrated schematically in Figure 4.7. With the Gaeltec catheter, minimum tonic, maximum peak and peak SPT pressures were all significantly greater when recorded from the posteriorly orientated strain gauge. The maximum tonic and peak UOS pressures from the sleeve catheter were, however, recorded from the anterior side-hole. These pressures were not only significantly greater than those recorded from any of the other side-holes, or from any Gaeltec sensor, but were also significantly greater than those of the posteriorly orientated sleeve sensor. The radial asymmetry observed with the sleeve catheter is illustrated by the compressed GR800 trace display in Figure 4.8. The greatest tonic UOS pressure is recorded from the anterior side-hole. The trace also demonstrates the slow recovery to baseline pressure of the sleeve sensor compared with the side-holes to following spontaneous dry swallows. The lowest sleeve catheter recordings were from the left and the left posterior side-holes. In contrast, minimum tonic UOS pressure was clearly greatest in sleeve sensor recordings (60 mmHg, Table 4.6a). The relatively abrupt rise in pressure when the sleeve sensor's proximal margin enters the UOS can also be observed in Figure 4.8.

Examination of UOS SPT tracings revealed that in lateral channels the zone of maximum tonic pressure tended to be located centrally within the high pressure zone. In one subject, no discrete zone of maximum pressure could be determined. The axial location of the maximum tonic pressure in the anterior and posterior planes in the remaining 49 subjects is listed in Table 4.6b. The anterior maximum pressure zone was located proximally in the UOS in 26 subjects, while the posterior maximum pressure zone was located distally in 22 subjects ($X^2 = 27.8$, $p < 0.001$). This axial asymmetry is illustrated in Figure 4.9 which shows a strain gauge

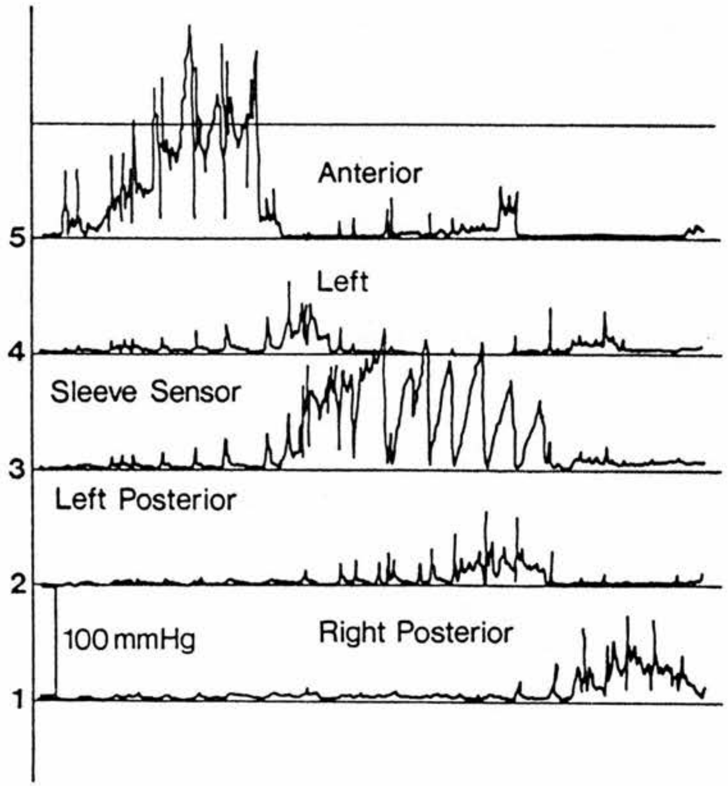


FIGURE 4.8 -

Sleeve Catheter UOS SPT Showing Radial Asymmetry with Greatest Maximum Tonic Pressure from the Anterior Side-Hole (P4)

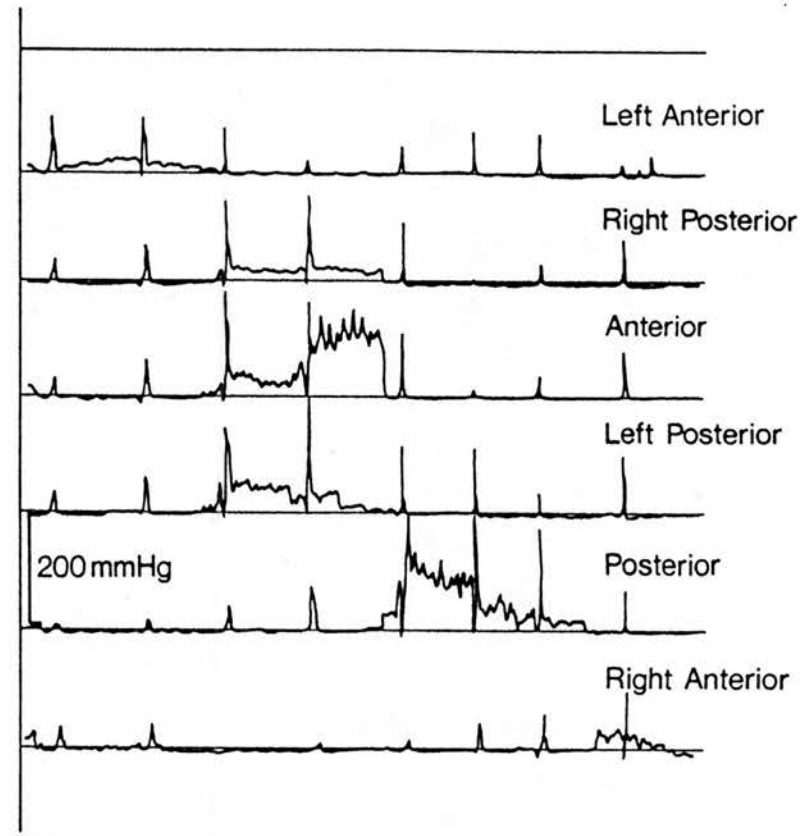


FIGURE 4.9 -

Gaeltec Catheter UOS SPT Showing Axial Asymmetry: Maximum Tonic Pressure is Proximal Anteriorly (P4) and Distal Posteriorly (P2) assembly station pull-through in a 25 year old male with a proximal high pressure zone anteriorly and a distal zone posteriorly. In this subject, the left posterior maximum tonic pressure is also proximally located. In the remaining subjects, both anterior and posterior maximum tonic pressure levels were located centrally within the zone of tonic UOS pressure.

An interesting sex difference was also observed. Significantly more males than females had a proximal maximum pressure zone anteriorly ($X^2 = 7.18$, $p < 0.01$) or a distal zone posteriorly ($X^2 = 3.87$, $p < 0.05$). In female subjects there was less evidence of axial asymmetry and the majority had more centrally located maximum tonic pressure segments. There was also a trend to higher wet swallow after-contraction pressures in female subjects (mean = 86 mmHg) than in males (mean = 71.6 mmHg, $t = -2.0$, $p = 0.053$). This difference is further considered in Section 4.6. There was no significant sex difference in any other UOS SPT parameter and the results were independent of cigarette smoking.

The Gaeltec catheter peak UOS pressure following dry swallows was greater where that catheter was used first ($t = 2.7$, $p = 0.01$). Otherwise, order of study made no significant difference to the results obtained. The effects of age are considered in Section 4.6 where results of a group of volunteers aged 60 years and over are described. UOS maximum tonic pressure showed a positive correlation with LOS SPT tonic pressure (r_s 0.24, $p < 0.05$ sidehole; $r_s = 0.35$, $p < 0.01$ Gaeltec and sleeve sensor), and with peak inspiratory LOS SPT pressure ($p < 0.05$ for all three UOS tonic pressure measurements). There was no significant association of tonic UOS pressure with LOS RPT pressure.

4.4.5 Results - Pharyngo-oesophageal Motility

One subject consistently swallowed water boluses as double swallow events and her results were, therefore, excluded from the data analysis. Results in the remaining 49 subjects are shown in

Table 4.7. A sample tracing of normal wet swallow patterns recorded by the Gaeltec catheter with three strain gauges in the UOS is shown in Figure 4.10. Pharyngeal and UOS after-contraction pressures were significantly greater when recorded with the Gaeltec catheter than with the sleeve side-holes. Mean sleeve sensor after-contraction pressure was almost identical to that of the Gaeltec catheter. Significantly lower minimum UOS relaxation pressures were recorded with the sleeve catheter although the standard deviation of relaxation pressure differences was large compared with other parameters (Figure 4.11). The side-hole channels had the shortest time to minimum relaxation ($p < 0.05$ vs both sleeve sensor and Gaeltec catheter) and the sleeve sensor was much the slowest to register peak UOS after-contraction ($p < 0.001$ vs both other recording methods), confirming the observation of dry swallow patterns during sleeve sensor SPT of the UOS (Figure 4.8). The inter-relationships of motility parameters and tonic UOS pressure are considered in Section 4.6. Comparison of the normal wet swallow parameters summarised in Table 4.6 with those of the patients with cervical symptoms listed in Table 4.3, Page 111, indicates that pharyngeal and UOS contraction amplitudes in the latter are considerably greater than those of normal subjects. These differences are explored in greater detail in Section 6.4.

4.4.6 Results - Repeat Manometry

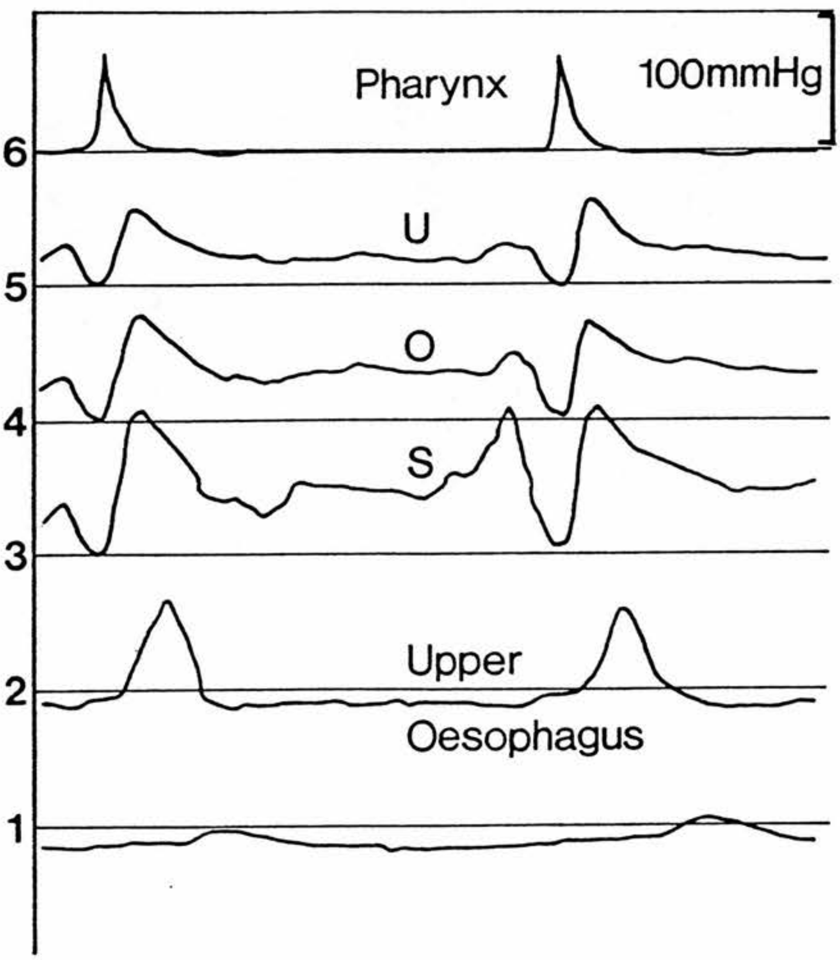
Results of repeat manometry in 15 subjects at a mean interval of 12 weeks are shown in Table 4.8 and Figure 4.12. Mean LOS pressure initial and repeat values show very little difference among the three methods of assessment. Inspection of the corresponding coefficients of repeatability, however, indicates clearly that LOS RPT measurements are the least repeatable (CR = 0.73), while LOS tonic SPT pressure is the most consistent (CR = 0.27) and shows the greatest correlation of initial and repeat values (r_s = 0.82, $p < 0.001$). Initial and repeat estimations of LOS length were also similar (initial = 3.5 ± 1.4 cm, repeat 3.2 ± 1.0 cm).

TABLE 4.7 - Single Water Swallows: Gaeltec and Sleeve Catheters in 49 Healthy Volunteers

	GAELTEC CATHETER		SLEEVE CATHETER SENSOR		SLEEVE CATHETER SIDE-ORIFICE	
	X	SD	X	SD	X	SD
Pressure (mmHg)						
- peak pharynx	36	17	-		21**	10
- UOS relaxation	7.1	5.3	4.6*	6.3	3.3*	6.5
- UOS after-contraction	76	24	74	22	55**	19
Time (secs) to						
- maximum relaxation	1.06	0.49	0.97	0.29	0.92*	0.27
- peak after-contraction	2.14	0.70	2.41**	0.53	2.14	0.49
- end of swallow complex	4.34	1.16		4.04*	0.84	

* p<0.05, ** p<0.001 vs Gaeltec

FIGURE 4.10 - Normal Water Swallow Motility Pattern (Gaeltec Catheter)



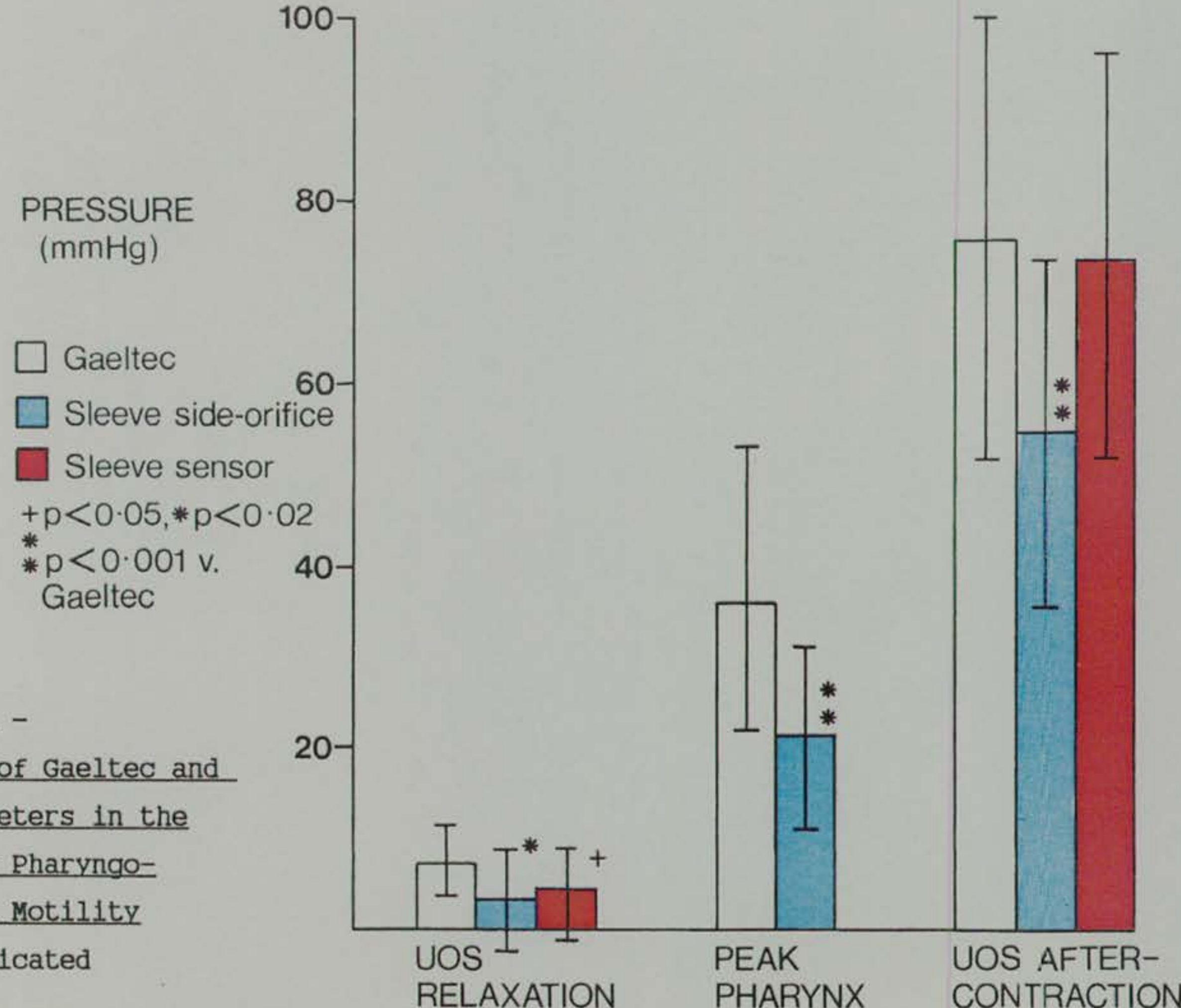


FIGURE 4.11 - Comparison of Gaeltec and Sleeve Catheters in the Analysis of Pharyngo-oesophageal Motility

SDs are indicated

TABLE 4.8 - Repeat Manometry in 15 Subjects

(Pressures in mmHg)	FIRST MEAN	SECOND MEAN	MEAN DIFF$^{\emptyset}$	95% CI OF MEAN DIFF	Z	r_s	CR
LOS RPT pressure	17	16	1.3	-5.8 to 8.4	0	0.02	0.73
SPT pressure - tonic	13	14	-1.4	-3.4 to 0.6	-1.45	0.82**	0.27
- peak	30	31	-0.5	-7.2 to 6.2	-0.07	0.38	0.39
Peristaltic amplitude	64	50	13.5	3.1 to 24.8	-2.22^{+}	0.75**	0.33
UOS SPT tonic - sleeve sensor	85	89	-4.7	-23.4 to 16.1	-0.60	0.62*	0.39
- side hole	63	60	2.6	-8 to 13.2	-0.45	0.76**	0.31
- Gaeltec	42	41	1.7	-3.3 to 6.6	-0.14	0.81**	0.21
UOS SPT peak - sleeve sensor	140	113	26.4	-3.9 to 56.4	-1.54	0.60^{++}	0.42
- side hole	128	120	8.1	-11.3 to 27.5	-0.48	0.75**	0.28
- Gaeltec	102	85	16.5	-4.9 to 37.9	-1.68	0.27	0.41
Wet swallow pressure (Gaeltec)							
- peak pharynx	35	38	-2.1	-12.7 to 8.5	-0.40	0.24	0.53
- UOS relaxation	7.9	7.5	0.3	-3.7 to 4.4	-0.17	0.22	0.96
- UOS after-contraction	69	81	-11.8	-29.7 to 6.1	-1.31	0.49^{+}	0.43
Wet swallow duration (secs)	4.58	3.93	0.65	-0.17 to 1.47	-1.41	0.12	0.34

$^{\emptyset}$ Mean difference = first value - second value. $^{+}$ $p < 0.05$, $^{++}$ $p < 0.02$, * $p < 0.01$, ** $p < 0.001$

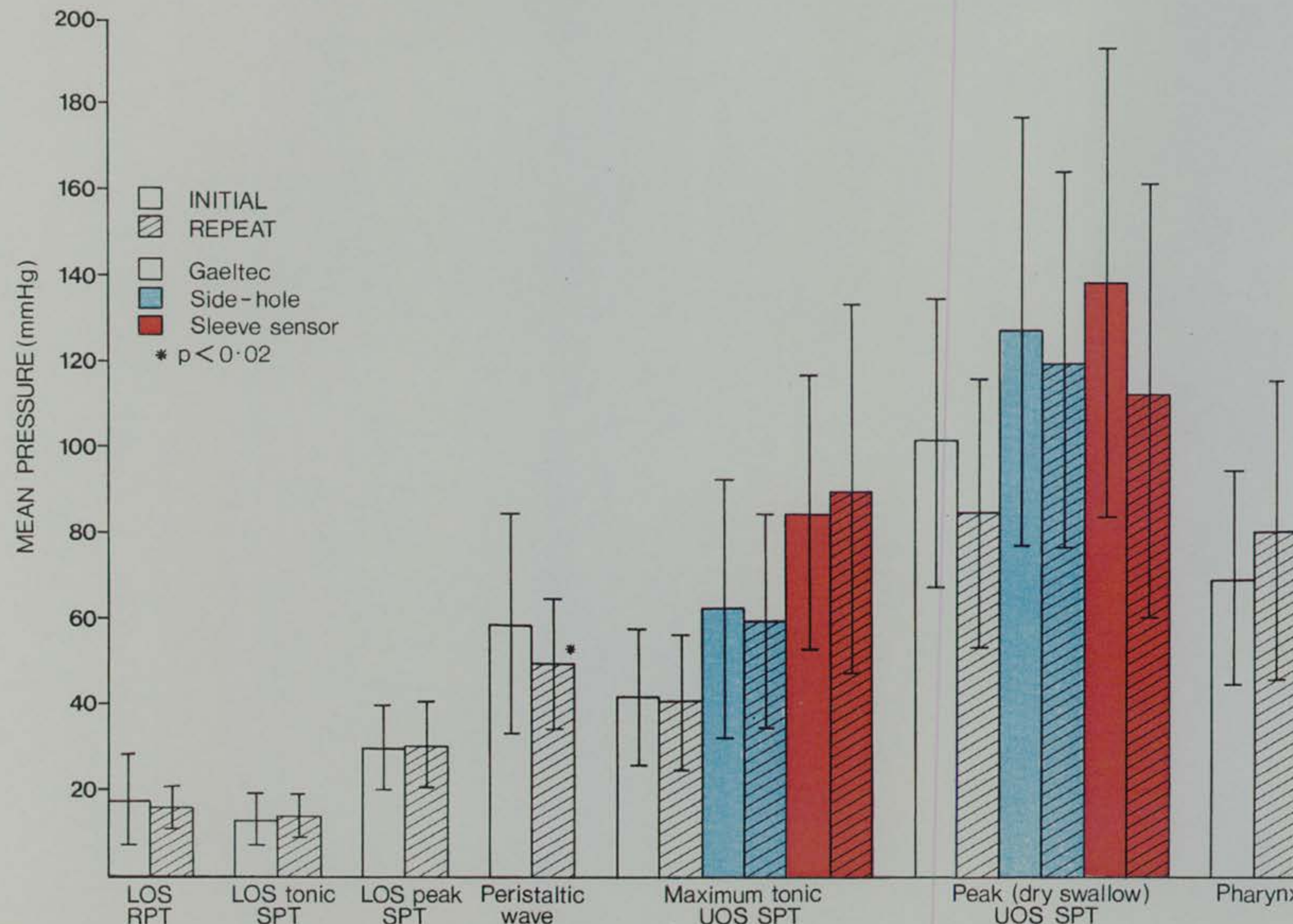


FIGURE 4.12 - Comparison of Initial and Repeat Manometric Findings (SDs are indicated)

Mean peristaltic amplitude was the only parameter to show a significant difference in magnitude or repeat examination although there was a good correlation of initial and repeat values (r_s = 0.75). The least variable parameter of tonic UOS pressure was SPT pressure recorded by the Gaeltec catheter (CR = 0.21, r_s = 0.81, $p < 0.001$)). Wet swallow duration was moderately consistent (CR = 0.31) but all wet swallow pressures showed considerable variation. This variation, as in the comparative study of the Gaeltec and sleeve catheters, was greatest for wet swallow relaxation pressure (CR = 0.96) and the correlation of initial and repeat wet swallow pressures was significant only for UOS after-contraction.

4.4.7 Discussion

The present study is the first systematic comparison of the performance of a sleeve device with that of a strain gauge assembly in the recording of pharyngo-oesophageal motility. The data obtained from the strain gauge assembly in the LOS and oesophageal body are also included in this report, for three reasons. Firstly, there are very few reports of strain gauge manometry at these sites (Weihrauch and Foerster 1977, Humphries and Castell 1977, Kaye et al 1977, Rex et al 1988) and the assemblies have been criticised on grounds of expense, fragility of the sensors and rigidity of the tube (Dodds et al 1976, Wingate 1983). Also, most manufacturers are able to produce only a three-sensor probe or a circumferential probe of broad diameter. Secondly, there have been several reports that LOS incompetence and consequent GOR may influence motor function in the upper oesophagus (Hunt et al 1970, Smiley et al 1970, Henderson et al 1976). Thirdly, the optimum method of scoring tonic UOS pressure has not been established and comparative studies of different methods of LOS pressure measurement are, therefore, of interest.

The continuous pull-through method of LOS pressure measurement was advocated by Dodds et al (1974) because of the difficulties encountered in scoring the oscillatory trace of SPT methods. This oscillation had previously been attributed to the influence of extra-oesophageal respiratory pressure changes (Vantrappen et al 1960). Later studies established that pressure oscillation was a movement effect due to oesophageal shortening on inspiration (Sullivan 1974). This axial movement is of the order of 0.5 cm, and pressure fluctuations are greatest in the subdiaphragmatic segment of the oesophagus (Welch and Gray 1982). The transmission to the LOS of the inspiratory diaphragmatic contraction may also make a small contribution to the pressure rises on inspiration - the manometric equivalent of the diaphragmatic pinchcock. Thus, at the end of inspiration, only the intra-abdominal segment of the high pressure zone functions as a barrier (Vantrappen et al 1960). At end-expiration, the whole LOS functions as a barrier. While having the advantage of the elimination of respiratory fluctuation, there is still considerable debate about the value of end-expiratory RPT measurements of LOS pressure. Some authors have questioned the value of any form of LOS pressure measurement on the basis of poor repeatability (Chattopadhyay and Pope 1979) or poor discrimination between normal subjects and those with GOR (Winans and Harris 1967). It is not surprising, therefore, that Kaye and Showalter (1974) applied the Heisenberg uncertainty principle to LOS pressure measurement following the demonstration that measured pressure rose with catheter diameter, ie that the catheter records resistance to stretch ('yield pressure') and thus itself alters the measured variable. In a detailed analysis of the effect of catheter diameter on the discriminant value of LOS pressure recordings, Biancani et al (1973) concluded that the optimum discrimination of competent and incompetent sphincters was achieved by either a very fine-bore (2.5 mm) catheter, or a very large bore (10 mm) catheter. Both this finding and the known relationship of LOS pressure to catheter diameter suggest potential advantages in the recording of LOS pressures with the 2.8 mm strain gauge assembly used in the present study.

In 1980, Meyer and Castell proposed that the choice between RPT and SPT measurements of LOS pressure be left to the discretion of the investigator. The group's preliminary findings in 50 normal subjects were that the results of both methods were almost identical (Nelson et al 1983). Their subsequent report of 95 healthy volunteers (Richter et al 1987) showed a mean end-expiratory RPT pressure of 29 $\pm$ 12 mmHg (X $\pm$ SD) and a mean mid-respiratory SPT pressure of 24 $\pm$ 10 mmHg (r = 0.70). The present results using a similar Arndorfer catheter in patients with cervical symptoms (Table 4.1, Page 93) showed a much greater difference between the two methods when the mid-respiratory pressure was calculated over the whole length of the LOS. In patients studied by the strain gauge assembly (Table 4.2, Page 102) the difference between mean RPT (29 mmHg) and mean SPT (19 mmHg) was twice as great as the 5 mmHg difference reported by Richter et al, despite the fact that LOS SPT pressure was derived from the zone of maximum tonic sphincter pressure. In the present larger study of healthy volunteers, however, there was little difference between mean RPT (18 $\pm$ 9 mmHg) and SPT (16 $\pm$ 7 mmHg) measurement (Table 4.4a). This concordance may be due to a reduction in LOS irritation when the RPT is performed with a fine-bore catheter. Peak (end-inspiratory) pressures were almost twice as great. Although in the present study the correlation of RPT and tonic SPT measurements was similar to that of Richter et al (r_s = 0.63), the reporting of means and of correlation coefficients conceals a variability of over 40% between the two methods (CR = 0.42).

In a study of 18 normal subjects, Welch and Drake (1980) found that RPT pressure was the most variable and least well correlated with other pressures of any LOS measurement. In the present study also, there was a closer correlation of peak and tonic SPT pressures (r_s = 0.71) than of RPT with SPT pressures but this does not per se constitute an argument for SPT measurement: both parameters are derived from the same segment of trace and their correlation might, therefore, be due to the agreement of two equally unsatisfactory measurements. A stronger case for SPT pressure measurement can be based on the results of the repeat manometric study (Table 4.8) which show that for RPT, CR = 0.73, whereas tonic SPT pressure was much more repeatable (CR = 0.27). Similarly, Welch and Drake (1980) found that increasing the number of RPTs performed tended to increase rather than to decrease the variability of this parameter. Chattopadhyay and Pope (1979) also found a variability of up to 43% in successive LOS RPTs in 11 healthy subjects. The variation in RPT pressure is almost certainly due to a variation in the completeness of expiration and to subjects' varying ability to suspend respiration for 20 to 30 seconds. Thus with RPT measurements there is no doubt about which point to record (the peak of the pressure curve) but the resultant pressure appears to be so variable as to be of limited value.

With SPT pressure measurements, the situation is very different. The pressures are repeatable and reasonably well correlated but it is not known which pressure should be selected from the oscillating wave (Dodds et al 1974). Unlike RPT measurements which are made during a single respiratory cycle, SPT pressures are derived from three to four stations with at least 20 sec at each station (Welch and Drake 1980). Inspiratory pressure peaks may be averaged but some advocate the exclusion of large peaks which are obviously due to deep breathing (Welch and Drake 1980) a policy which might be expected to increase inter-observer variation and which may exclude the pinchcock effect of the diaphragm on deep inspiration (Vantrappen et al 1960). These peaks of inspiratory SPT pressure may make a significant contribution to physiological UOS competence (Welch and Gray 1982) but others still regard the minimum expiratory points to be of greater importance with respect to the prevention of GOR (G Vantrappen, personal communication 1988). As some distal expiratory points may represent the return of the sensor to the stomach (Sullivan 1974) and as in many subjects the magnitude of end-expiratory pressure is little higher than the intragastric baseline, the validity of this parameter remains questionable.

The ability of the GR800 recorder to compute the mean pressure from a series of asymmetrical oscillations represents a major methodological advance. The mean pressure derived takes account of both peak inspiratory and end-expiratory points and is a much more meaningful parameter than the traditional 'mid-respiratory' point - ie the pressure level drawn at the midpoint of the respiratory cycle. Because of the shorter duration of the inspiratory phase, the traditional mid-respiratory line may overestimate tonic pressure and this may have contributed to the greater mean mid-respiratory pressure in normal subjects reported by Richter et al (1987) of 24 mmHg compared with 16 mmHg in the present study (Table 4.4a) particularly as the mean peak inspiratory pressure was only 5 mmHg lower in the present study than in that of Richter et al. Another factor contributing to the generally lower LOS pressures reported here is the performance of the GR800 recorder, which had a bias to record LOS pressures which were a few mmHg lower than those of the chart recorder (Table 4.2, Page 102). In addition, Richter's group performed LOS pressure measurements from only 4 side-holes at 90^{o} orientation, rather than from 5 or 6 strain gauges at 60^{o} orientation.

Radial asymmetry of the LOS was observed by Pope (1967) but was first studied in detail by Winans (1977) in a group of 10 normal subjects, who showed evidence of localised increase in pressure in the left posterior segment, which he attributed either to the lateral pressure exerted by the diaphragm as the oesophagus inclines to the left before joining the stomach, or to the sling-like fibres of the gastric fundus at the cardiac incisura. Welch and Drake (1980) also include a detailed analysis of radial LOS asymmetry in their report of 18 healthy subjects. As in the present report, their findings indicate that the lowest pressures are recorded from the right posterior segment (Figure 4.4). Nonetheless, it is hard to justify their conclusion that future studies should be unidirectional with a known orientation and that the remaining radial pressures be calculated from their published composite illustration of a relatively small number of subjects. It must be remembered, however, when interpreting average peak or tonic pressures from several radial channels that the derived value does not represent a true anatomical point, owing to the axial asymmetry of the LOS which can be seen where several sensors are located at the same level, as in the present study. Some workers prefer, therefore, to calculate the mean of the peak pressures for each station and to report the 'peak of the means' as the maximum tonic pressure (J Janssens, personal communication, 1987). Neither method takes account of the length over which the pressure is applied. Pope (1967) believed that the ideal sphincter pressure measurement was of the radial force required to open a closed sphincter when applied along the entire length of the sphincter. Even this parameter (which is unattainable manometrically as once the catheter is in position the sphincter is, by definition, no longer closed) does not take account of LOS pressure changes over time. The maximum tonic LOS pressure in the present study was computed accurately over time, averaged from six radial sensors and showed least intrasubject variation over a period of several months. It is recommended that this LOS parameter be adopted for clinical use where computerised recording is available, as the fine-bore nature of the catheter is likely to make the measurement a good discriminant of LOS incompetence (Biancani et al 1973) and its stability over time will allow meaningful comparison of subject groups. Previous studies claiming greater discrimination by peak or trough pressures may, in effect, refer more to the stretch response of the sphincter to the catheter than to the physiological LOS resting pressure, although it remains possible that such responses are important in the presence of abnormal LOS motor function.

It has been suggested recently that assessment of LOS relaxation during studies of oesophageal body motility is of no value, except in the presence of total aperistalsis (Howard et al 1988a). Sullivan (1974) suggested that LOS relaxation was a movement artifact. Dodds et al (1974) concluded however, that a genuine relaxation could be observed but that its measurement required a series of recording sites proximal to the LOS sensor which would record intragastric pressure following orad movement of the LOS during swallowing. An alternative assessment was the performance of an RPT during the anticipated interval of LOS relaxation (Dodds et al 1976). The presence of genuine relaxation was later confirmed by Asoh and Goyal (1978) during electromyographic study of the opossum LOS. In the present study, LOS relaxation was studied with a single LOS sensor in only 15 subjects. Kelley et al (1960) demonstrated that timing of LOS relaxation also depends on the recording site relative to the diaphragmatic hiatus and on the recording sensor: the time intervals from onset of relaxation to minimum relaxation pressure and to the end of the relaxation interval when recorded with a balloon catheter close to the diaphragmatic hiatus were similar to those of the present study, ie 5 and 10 sec respectively. It is probable that these time intervals will be rendered meaningful only when combined with an independent method for the assessment of sphincter-on-catheter movement but although the minimum pressure recorded during LOS relaxation may in part be a descent artifact, this measurement is in routine clinical use in the determination of completeness of relaxation in the diagnosis of achalasia. The present results in normal subjects of a mean residual pressure of 2 mmHg (reduction of 87%) are in keeping with most other reports of normal LOS relaxation pressure. An abrupt, early fall in LOS pressure was frequently observed, corresponding to the 'swallow breath' inspiration (Goyal and Cobb 1981), as LOS pressure was usually assessed above the respiratory inversion point. The present results, like those of Berte and Winans (1977), show evidence for a positive correlation of tonic pressure in the lower and upper oesophageal sphincters and, therefore, provide no support for the proposed relationship of GOR and UOS hypertonicity in normal young and middle aged subjects. In patients with pathological GOR, however, the findings may be somewhat different, and the association of GOR and UOS function is considered in detail in Section 5.1 and Section 5.2.

A wide range of peristaltic amplitudes was observed (23 to 226 mmHg, Table 4.4a), and peristaltic pressure was the only parameter to show a significant difference on repeat testing (mean difference = 13.5 mmHg, $p < 0.05$, Table 4.8). Even in studies of as few as ten subjects, a wide range of normal peristaltic amplitude has been previously observed, eg 58 to 181 mmHg (De Vault et al 1987) or 55 to 168 mmHg (Dalton et al 1988). In their group of 95 volunteers, Richter et al (1987) found a mean peristaltic amplitude in the distal oesophagus of 99 mmHg (SD = 40), ie somewhat greater than the present mean amplitude of 87 mmHg (SD = 37) but with a similar distribution. The upper limit of normal amplitude has important implications for the definition of oesophageal motor disorders, and Richter et al concluded from their wide range of normal values that this limit should be at least 180 mmHg.

There have been a few previous reports of normal peristalsis recorded by intraluminal strain gauges since it was demonstrated that results were comparable to those of perfused catheters, provided that a high infusion rate was used (Dodds et al 1972a, Hollis and Castell 1972). Pope and Horton (1972) used a mercury-in-silastic strain gauge attached to a plastic sphere of variable diameter to measure the force of peristaltic propulsion which was found to be directly related to the volume of the attached sphere. Humphries and Castell (1977) in a study of ten subjects recorded a mean distal amplitude of 70 mmHg and demonstrated a close correlation of amplitude with the slope of the wave upstroke (dP/dt). Stacher et al (1982) used strain gauges to investigate 8 normal subjects and described a similar mean amplitude (78 mmHg) as did Weihrauch et al (1980a) who found a mean amplitude of 73 mmHg in a much larger series of 40 subjects studied with a 6 mm diameter circumferential intraluminal transducer. The present finding of a mean amplitude of 87 mmHgin normal subjects is, therefore, similar to that of Clouse and Staiano (1983) with a fine-bore perfused catheter (85 ± 27 mmHg). These results lie between the findings of Richter et al (1987) with a perfused catheter and those of several studies with intraluminal strain gauges. Much of the discrepancy among these reports can be attributed to the apparent biological variation, both intersubject and intrasubject, of peristaltic parameters. In the present study the repeat testing of 15 subjects indicated a variability of 30% (CR = 0.33, Table 4.8). Dalton et al (1988) used a different statistical method to assess intrasubject variability but with a similar result (27%). Part of the biological variation may be related to the varying levels of stress experienced during testing. The influence of emotional stimuli on oesophageal body contraction is well-recognised (Nagler and Spiro 1961, Clouse et al 1987) and stress has been shown to produce a significant increase in normal subjects (Anderson et al 1989).

The velocity of the peristaltic wave (3.1 $\pm$ 0.7 cm/sec) in the present study is similar to that reported by others at a similar distal location (Ask and Tibbling 1980, Richter et al 1987). Like the amplitude, the velocity of the peristaltic wave is subject to methodological variation, although the pressure profile of the tubular oesophagus is more easily distinguished and varies less than does sphincter pressure when subjected to fully-automated computer analysis (Feussner et al 1987). One important variable is the level at which peristalsis is recorded. Just above the gastro-oesophageal junction lies the vestibule (the radiological 'ampulla') and the velocity of the peristaltic wave is considerably reduced at this site (Vantrappen et al 1960). Above this level, there is a tendency for the wave to accelerate (Ask and Tibbling 1980), reaching a peak velocity 7 cm above the LOS of almost 5 cm/sec compared with a velocity of only 2 cm/sec in the vestibule (Humphries and Castell 1977). The distribution of pressure along the oesophageal lumen, however, follows a concave distribution with a trough at 17 to 20 cm above the LOS.

Similarly, Kahrilas et al (1988b) calculated from manofluorometric studies that the minimum amplitude required to prevent retrograde escape of barium was 25 mmHg in the distal oesophagus but only 12 mmHg more proximally, a difference the authors attributed to differences in the compliance of the oesophageal segments distal to the advancing bolus.

Other methodological factors contributing to the variability of peristaltic amplitude among different series are the catheter diameter (Richter et al 1987), the temperature of the water bolus and the inter-swallow interval (Ask and Tibbling 1980, Stacher 1985, Vanek and Diamant 1987). Increasingly, workers are using 5 ml boluses of water at ambient temperature with 15 to 20 sec intervals. In patients studied with both the Arndorfer and the Gaeltec catheter, the mean peristaltic amplitude was 12 mmHg less with the 2.8 mm Gaeltec catheter (Table 4.3, Page 111) but no further conclusions on the effect of catheter diameter can be drawn from comparison of the present results with those of other studies, because of the presence of other methodological variables. Thus, while the mean peristaltic amplitude in Richter's series with a 4.5 mm diameter catheter was greater than that of the present study, the use of an even broader (6 mm) circumferential strain gauge (Weihrauch et al 1980a) resulted in a lower mean peristaltic amplitude than in the present study.

De Vault et al (1987) using an on-line computer linked to a chart recorder showed that the intrasubject variation in velocity was greater than that of contraction amplitude but that the most variable parameter was the duration of contraction. While Richter et al (1987) attributed the poor correlation of amplitude and duration in part to factors of latency or neurohormonal control, it is probable that much of the variation is due to measurement error. The previous comparison of simultaneous chart and GR800 results showed that the variability of duration measurement was 16% (Table 4.2, Page 102). Vantrappen's group (personal communication 1988) have defined the onset of duration as the point where the extrapolated steepest upstroke intersects with the oesophageal baseline, ie ignoring the slurring at the onset of the peak which is due to the passive transmission of pharyngeal pressures through the swallowed bolus and not related to the contraction itself (Vantrappen et al 1967). Two alternative end-points are, however, described - one the extrapolated steepest downstroke and the other the final point of intersection of the descending limb and the end-expiratory baseline pressure. These definitions are in practice much more readily achieved with a chart recorder, when extrapolated lines can be drawn on the tracing. Once fully automated computer analysis becomes available, the duration measurements with the GR800 will be very precise as the temporal resolution is 0.01 sec and the determination of the point of maximum dP/dt is a readily automated function. In manual analysis of computer displays, the extrapolations can only be estimated. Duration data from the lower oesophagus are not, therefore, included in the present report but the wave in the upper oesophagus has a readily determined onset and endpoint. The correlation of amplitude in the distal oesophagus and duration of the upper oesophageal wave in the present study was, like the correlation of distal amplitude and contraction in Richter's study, only weakly positive ($r_s = 0.30$, $p < 0.01$). The correlation of wave velocity and peristaltic amplitude was ultimately studied in a total of 31 normal subjects (including most of the older control subjects described in Section 4.6) and was found to be even less significant ($r_s = 0.25$, $p = 0.09$). In the present series of healthy subjects, there was no obvious association of peristaltic amplitude with age, but in their larger series, Richter et al (1987) found that peristaltic amplitude increased with age until the fifth decade. The question of age and peristaltic amplitude is further considered, therefore, in Section 4.6. In normal subjects, there appears to be no association of peristaltic amplitude with LOS pressure, although in oesophagitis patients, a deficiency of peristaltic contraction likely to lead to impaired volume clearance has been described (Kahrilas et al 1988b).

The respiratory fluctuation in tonic pressure in the UOS follows a similar pattern to that of the distal LOS. The inspiratory UOS pressure increase contrasts with the inspiratory fall in the adjacent cervical oesophagus (Goyal et al 1970) but, unlike the LOS, the principal methodological problems encountered in UOS manometry are the marked radial asymmetry (Winans 1972) and the accurate recording of the deglutition complex. The axial asymmetry is such that even the shape of the recording catheter is reported to alter significantly the observed pressures so that an oval perfused catheter conforming to the slit like configuration of the UOS records considerably lower mean maximum tonic pressure than a similar round catheter (Green et al 1986, Kahrilas et al 1987a). The upward movement of the laryngopharyngeal complex during swallows produces so great a sphincter-on-catheter movement that some workers have claimed that a single sensor in the high pressure zone at the onset of deglutition will be outwith the UOS during most of the ensuing swallow sequence (Isberg et al 1985a). The sleeve sensor (Dent 1976) was modified for use in the UOS to overcome this problem while strain gauges were first used over 30 years ago to assess the rapid events in the pharyngo-oesophageal segment on deglutition (Fyke and Code 1955).

There have been studies of UOS function comparing different types of strain gauge (Rex et al 1988), comparing strain gauges with perfused catheters (Dodds et al 1975, Kaye et al 1977) comparing a sleeve with perfused catheters (Kahrilas et al 1987a) and describing the combined use of both the sleeve catheter and a pair of pharyngeal strain gauges (Kahrilas et al 1988a) but there has been no previous systematic comparison of the sleeve catheter with a strain gauge assembly. In the present study, certain reported aspects of UOS function, in particular the radial asymmetry, were qualitatively confirmed by both methods (Figure 4.7). Both catheters recorded maximum pressures, as expected, in the anteroposterior plane but the sleeve catheter readings were greater from the anteriorly orientated side-hole than from the posteriorly orientated sleeve diaphragm. Since the greatest strain gauge pressures were recorded from the posterior plane, and use of a multilumen side-hole catheter is also reported to yield greater posterior than anterior pressures (Hellemans et al 1981), this is an important observation as it suggests that the sleeve sensor may be slightly less sensitive to tonic pressure than an equivalent side-hole. An alternative explanation might be the occasional rotation of the sleeve sensor into the postero-lateral plane, noted on catheter withdrawal, but this would be expected to reduce the anterior recordings by an equivalent amount. Kahrilas et al (1987a) observed significantly lower pressures in both the anterior and posterior planes when comparing a sleeve sensor with eight- and four-lumen side-hole assemblies. This was attributed to the RPT technique used with the side-hole catheters but may also have been due in part to differences in pressure sensitivity between the sleeve sensor and the perfused holes. Kahrilas also reported no significant change in measured pressure with the sleeve sensor once the sensor entered the UOS, for a length of 5 cm. Since Kahrilas et al orientated the sleeve in the anterior plane, this is somewhat surprising, as the pattern of anterior axial asymmetry is such that the distal pressures on SPT in this plane would not be expected to be as high as those of the more proximal zone of maximum tonic pressure. In the present study a minimum tonic pressure, albeit much greater than by other methods, was clearly registered (Table 4.6a), implying that the entry of the sleeve to the UOS does not produce as abrupt a pressure rise as has been previously claimed.

A further novel observation is that the pattern of axial asymmetry is more marked in males than females. Welch et al (1979) and Gerhardt et al (1980b) observed that maximum UOS pressures were located more distally in the posterior than the anterior plane. This finding is confirmed in the present study (Table 4.6b). The axial structures contributing to the upper high pressure zone outwith the 1 cm zone corresponding to the crico-pharyngeus muscle are not known, but in view of the established pattern of axial asymmetry it seems that the upper oesophageal and thyropharyngeal fibres must both contribute. An anatomically identified circular band of upper oesophageal fibres was thought by Zaino et al (1967) to comprise a major part of the UOS. Such a band would, however, exert a circumferential force and would not explain the finding of a greater sphincteric force below the cricopharyngeus in the anterior plane. The anterior insertion of the longitudinal bands of the oesophageal musculature (Birmingham 1899) and the broad posterior lamina of the cricoid cartilage which lies against the anterior wall of the UOS may also, therefore, be important, particularly in view of the male pubertal growth spurt of the laryngeal cartilages. The angle of attachment of the cricopharyngeus has also been proposed as a contributory factor (Welch et al 1979). Any functional sex difference in this area is, of course, of great interest due to the male preponderance of both pharyngeal (Zenker's) diverticula and of pharyngoceles.

Both the sleeve and the Gaeltec catheters produced similar patterns of radial pressure, but the magnitude of the recorded pressures were significantly different. The sleeve sensor values were higher than those previously reported (Cook et al 1987, Kahrilas et al 1987a and 1987b), in part due to the calculation of mean pressure throughout the respiratory cycle by the GR800. Other reports cite end-expiratory pressure. Although the sleeve sensor recorded significantly greater pressure than the mean side-hole value, analysis of radial pressures shows that this was an effect of orientation rather than of performance (Table 4.6a). This deduction would also explain the repeatability of tonic UOS pressure which was almost twice as poor with the sleeve sensor (CR = 0.39) as with the circumferential sampling of the Gaeltec sensors (CR = 0.21, Table 4.8). Where single sensor repeatability has been studied, posterior pressure is more consistent than any other single orientation (Gerhardt et al 1980b) but the unidirectional nature of the sleeve clearly makes it more likely to pressure fluctuation than circumferentially derived pressures.

Rex et al (1988) compared the repeatability of three radially orientated strain gauges with a circumferential sensor and found repeatability to be twice as good with the circumferential sensor. The present six-sensor assembly appears to compare favourably on repeat studies with the circumferential probe in Rex's investigation, although the mean tonic pressure was 25 mmHg less (40 mmHg). This, and some of the variation between the sleeve and the Gaeltec catheters, is likely to be an effect of catheter diameter as the assemblies used by Rex et al were 5.5 or 6 mm diameter. Weihrauch et al (1980b) used a 6 mm circumferential transducer and recorded average pressures in excess of 100 mmHg during UOS RPT in 119 normal subjects. A similar mean pressure (92 mmHg) was found by Castell et al (1988) during UOS SPT with an annular intraluminal transducer (diameter unstated). These forces appear to be of unphysiological proportions, likely to compromise sphincteric blood flow (Christensen 1983) and may represent a striated muscle stretch response. On the other hand, even using the 2.8 mm assembly in the present study, a very wide range of average maximum tonic pressure was found (15 to 93 mmHg), similar to sleeve sensor pressures reported in eight subjects by Kahrilas et al (1987b) of 16 to 118 mmHg. The present sleeve sensor range was 24 to 163 mmHg, due both to the different method of computing tonic pressure referred to above and to the very much greater number of subjects studied. It is possible that in some subjects pressures were augmented by the stress of the investigation: Cook et al (1987) demonstrated that acute stress could produce rises of 12 mmHg in tonic UOS pressure. In the present study the UOS SPT was performed after an examination of LOS and oesophageal body motility and it is unlikely that even this modest increment would obtain. What is certain is that the universally observed wide ranges of tonic pressure must cast doubt on the validity of studies reporting as few as five (Dodds et al 1975), seven (Fulbeck et al 1980), eight (Kahrilas et al 1987b and 1988a), nine (Gerhardt et al 1980b) or ten (Kaye et al 1977, Castell et al 1988) subjects, especially as there is in addition anintrasubject variability of up to 53% (Rex et al 1988). Only three recent studies have been reported involving more than 25 subjects (Weihrauch et al 1980b, Kahrilas et al 1987a and Rex et al

1988). It is this variability of UOS pressure which may have directed subsequent research to the extremely detailed analysis of swallow patterns in small groups of subjects. Such studies furnish useful insights into the physiology of deglutition and into potential manometric artifacts but cannot provide a meaningful database of normal values for clinical studies. Also, some of the mano-fluorometric investigations referred to below have involved a degree of radiation exposure to healthy subjects which in this country might be considered unacceptable on ethical grounds.

The present study of pharyngo-oesophageal motility represents the largest group of healthy volunteers investigated to date with modern manometric techniques. The results show important differences in the recording of deglutition pressures and kinetics between the two different recording catheters used (Table 4.7). Mean UOS after-contraction pressure recorded with the Gaeltec catheter (116 mmHg) was similar to the pressure (112 mmHg) reported by Dodds et al (1975). Rex et al (1988) report no data on UOS after-contraction. As expected, the rapid pharyngeal transients were better observed by a strain gauge than by a sleeve side-hole, although the latter was 1 cm higher in the pharynx. The mean hypopharyngeal contraction amplitude registered 3 cm above the maximum zone of tonic UOS pressure with a strain gauge was, however, only 36 mmHg (range 7 to 93 mmHg). This figure is somewhat surprising. Although Duranceau et al (1983a) report almost identical normal pharyngeal pressures using a triple-lumen catheter with a high infusion rate, standard texts (Goyal and Cobb 1981) and established authorities (Hellemans et al 1981) have reported pharyngeal contraction amplitudes in normal subjects of 100 to 200 mmHg. If Orlowski's finding of increased pharyngeal contraction amplitude in the distal pharynx (Orlowski et al 1982) is valid, then the 3 cm separation of the LOS and pharyngeal strain gauges in the present study is even more remarkable, as most workers have recorded pharyngeal pressure 5 cm above the UOS. Unfortunately, there are few comparable strain gauge data. Dodds et al (1975) showed a mean hypopharyngeal pressure of 128 mmHg in seven subjects studied with a 5 mm diameter strain gauge assembly, and Rex et al (1988) registered mean pharyngeal amplitudes of 153 mmHg with a radially sensitive 5.5 cm diameter strain gauge assembly and of 133 mmHg with a 6 mm diameter assembly in 30 volunteers. Kaye et al (1977) Weihrauch et al (1980b) and Isberg et al (1985a and 1985b) although reporting the use of strain gauges, give no quantitative data on pharyngeal contraction. In a study of patients with oculopharyngeal muscular dystrophy, however, Fradet et al (1988) reported normal pharyngeal contraction amplitudes in a group of 15 healthy controls. Two manometric systems were used - a triple-lumen perfused catheter linked to a chart recorder and a three-sensor strain gauge assembly linked to a computerised recorder. This is believed to be the only previous report of the use of a computerised, solid state manometric recording system, but the pharyngeal pressures recorded by the computer were not reported. The triple-lumen catheter system gave significantly lower pharyngeal pressure recordings in normal subjects, and the mean pressure (34 $\pm$ 5 mmHg) was very similar to that in the present study and to that of Duranceau et al (1983a). Similarly the reports of Kahrilas' group, although on occasion using strain gauges to record pharyngeal pressure to calculate velocity, do not include pharyngeal pressure values (Kahrilas et al 1988a). There is no evidence to suggest, however, that some authors may have excluded data on pharyngeal contraction because of the finding of inexplicably low amplitudes compared with reported values.

There are several possible explanations for the finding of markedly lower normal pharyngeal contraction amplitudes in the present study than in several previous reports with perfused systems and in the only two comparable strain gauge studies. It is possible that radial sampling affects were relevant as the pharyngeal pressures were all recorded in the left anterior plane. Winans (1972) found that the pharynx, like the tubular oesophagus, showed very little radial asymmetry but Kilman and Goyal (1976) state that pharyngeal pressures are not uniform and, like those in the UOS, are greatest in the anteroposterior plane. It is also unlikely, in view of the high pharyngeal contractions recorded occasionally in normal subjects and in patients (Table 4.3, Page 111 and Section 6.4), that the low value represents a fundamental deficiency in either the strain gauges or the GR800 recorder. Age is associated with an increase in pharyngeal contraction (Section 4.6) but, in previous reports, the normal volunteers had an age range similar to or less than those in the present study. There are, therefore, two principal explanations. The first is that the pharynx is even more sensitive to the diameter of the recording catheter than the UOS (itself more sensitive than the LOS, Lydon et al 1975). Indirect evidence to support pharyngeal catheter sensitivity is given in Section 4.5, where it will be seen that alterations in bolus consistency produce significant alterations in pharyngeal pressures.

Given the dense, protective sensory innervation of the hypopharyngeal mucosa it seems likely that catheter diameter is the other important factor in the observed difference. There is in addition the postulated phenomenon of chart recorder 'overshoot', referred to previously, and a speculative alternative explanation is that the previous reports of 100 to 200 mmHg contractions in the pharynx are themselves due in part to a recording artifact, because the speed of the pressure rate rise (slope of the upstroke) is so great in the pharynx that the wave is charted beyond the true pressure peak. The mean pharyngeal pressure in subjects studied twice (Table 4.8) was not significantly different between the two investigations, although the repeatability (CR = 0.53) was less than for tonic and peak UOS pressures. Nonetheless, the Gaeltec assembly as used in the present protocol seems to give consistent pressures which are about 25% of published normal values using different techniques. Even more than in the distal oesophagus (Richter et al 1987) there is, therefore, a need for each laboratory to establish its own normal ranges for studies of pharyngo-oesophageal motility.

In this study, the time from the onset of the swallow to the minimum relaxation pressure and peak UOS after-contraction were calculated in order to compare the rates of pressure fall and rise of the two catheters. The sleeve sensor showed a shorter time to minimum relaxation than the Gaeltec catheter, but the adjacent side-hole recorded an even greater rate of pressure fall despite a vendor specification of a rate of pressure fall of 200 mmHg/0.1 sec by the sleeve sensor. The time interval from the onset to the nadir of relaxation pressure was greater than 0.9 sec by both methods which must cast doubt on the validity of defining the onset of relaxation as the minimum relaxation pressure point (Kahrilas et al 1988a). In Kahrilas' studies the sleeve is positioned in the traditional way, ie with the upper margin of the sleeve above the upper border of the UOS. This is designed to prevent the sensor slipping out of the UOS during the laryngeal elevation on swallowing. In the present study, an attempt was made to compare the responses of the sleeve sensor and the side-holes by siting the upper margin of the sleeve and the adjacent hole at the level of maximum tonic UOS pressure. This more distal location of the sleeve was selected because of the slow recovery to baseline after swallow-induced relaxations when the sleeve was at a more proximal level which made it difficult to obtain reliable baseline pressure measurements. The slow rate of pressure rise at sites increasingly distal to the superior perfusion port of a sleeve has been demonstrated recently in the LOS by Wallin et al (1988). The definition of a reliable end-point of relaxation with the sleeve thus presents a problem. If, as in the present study, the sleeve does not straddle the sphincter but is sited with its upper margin in the mid-zone, then the duration of relaxation will be shortened by the faster rise rate of the proximal part of the sensor. With the upper margin of the sleeve within the hypopharynx, however, the registration of the descending wave of pharyngeal pressure by the upper, extra-sphincteric part of the sleeve will also prematurely shorten the duration of relaxation 'by a split second before the cricopharyngeus actually contracts' (Kahrilas et al 1987a). Whether or not this is of practical importance depends on what fraction of a second is actually involved (Paterson 1987). In their subsequent study (Kahrilas et al 1988a) the fraction was calculated to be 0.1 sec. The duration of wet swallow relaxation was 0.52 sec with a proximally sited side-hole which descended into the UOS on swallowing, and so a reduction of 0.1 sec represents a 20% reduction in relaxation interval. Although the wave of pressure traverses the hypopharynx at a speed of 9 to 25 cm/sec (Dodds et al 1975, Hellemans et al 1981, Kahrilas et al 1988a) the velocity across the UOS is much less (see Section 4.5) and the error entailed in estimating the end of relaxation as the point where the hypopharyngeal wave reaches the sleeve sensor correspondingly greater. In the present study, the time interval between the onset of pressure fall and the peak of the UOS after-contraction was measured and found to be greater than 2 sec by all recording methods (Table 4.7). The slow recovery to baseline (35 mmHg/sec) of even the proximal sleeve was reflected in the greater interval from onset to after-contraction time with the sleeve sensor (2.41 sec) but it must be remembered that the absolute time intervals recorded with both catheters in the present study may reflect the interval of laryngeal elevation more than the interval of true UOS opening, which can be assessed only with concomitant radiology (Kahrilas et al 1988a).

A further aim of the study beyond the comparison of the two catheters was to establish optimum definitions of temporal parameters for subsequent studies, in particular the relaxation interval. Kahrilas et al (1988a), operating under the technical constraints imposed by the sleeve catheter, classify only the period where UOS pressure is at its minimum level as the relaxation interval (approximately 0.6 sec), ie ignoring both the interval of pressure fall and, of necessity, the return to baseline pressure, since after relaxation a pharyngeal rather than a sphincteric contraction is registered as the sleeve protrudes into the pharynx. In the absence of these technical limitations, a more logical definition of the relaxation interval is the time period from the onset of pressure fall to the return to UOS baseline pressure (Figure 4.3, Page 119, No 2) particularly as it is not known which temporal component of the relaxation interval may be altered in disease states. The problem with this definition lies in the identification of the moment of onset of the pressure fall. The duration of relaxation has also been reported to vary with the precise UOS level at which it is recorded, being somewhat longer on strain gauge assessment in the distal UOS (0.93 sec) than in the upper part of the UOS (0.55 sec, Fulbeck et al 1980). UOS relaxation is preceded by an early, variably observed, low amplitude rise or 'E' wave which is caused by the laryngeal elevation which precedes deglutition (Sokol et al 1966a, Rex et al 1988, Cerenko et al 1989). The variable presence of this wave, which causes a brief (0.2 to 0.8 sec) episode of EMG spike activity, contributes a source of measurement error in the present study and it was therefore decided to exclude this wave, where present, from future calculations of relaxation intervals. For the purpose of subsequent comparison of water swallows with swallows of other substances (Section 4.5) the wet swallows were re-analysed. The duration of relaxation was calculated as the time from the pressure fall below baseline pressure, ie excluding the portion of the fall associated with 'E' wave descent, to the time where the UOS baseline was regained. The duration of after-contraction was calculated from this point to the end of the swallow complex. This method is also subject to error, as the UOS baseline fluctuates with respiration and Rex et al (1988) describe two arbitrary definitions of relaxation, ie below a level of 20 mmHg and of 40 mmHg above minimum relaxation pressure. There appears to be little advantage in this approach. The results may be more consistent but may also be misleading in the presence of incomplete UOS relaxation and will also be less meaningful as it is not known which level of residual pressure is of functional importance in respect of bolus passage. Similarly, although Kahrilas et al (1988a) found the duration of complete relaxation in a side-hole sited proximal to the UOS at the onset of swallowing to mirror radiological UOS opening most closely, this correlation does not of itself justify the argument that this is the optimum method of assessing sphincter relaxation in clinical studies. In pure manometric terms, movement effects may be dismissed as 'artifacts' but the fact remains that the impairment of laryngeal elevation on swallowing is a potent cause of dysphagia. Hyoid fixation by, for example, opening the mouth, results in considerable dysphagia, a finding which can be readily tested by comparing the ease of swallowing with the mouth open or closed. This may be even more marked in wet or solid swallows because of the loss of bolus 'engulfment' (Palmer at al 1988) when the sphincter undergoes 2 to 2.5 cm orad movement (Kahrilas et al 1988a). Postoperative hyoid fixation has also been shown to result in severe dysphagia (Hambraeus et al 1987). In other words, laryngopharyngeal movement should more properly be regarded as quintessential to the performance of swallowing, rather than as a manometric nuisance. For future studies in this thesis, therefore, the relaxation interval will be defined from the onset of the fall after the 'E' wave to the regaining of UOS baseline pressure recorded from a strain gauge at the station of maximal UOS pressure at the onset of the swallow, bearing in mind that some of the relaxation pattern so defined will be due to a descent of the transducers within the sphincter. It is proposed that in most normal subjects studied with the Gaeltec assembly, this movement is not so great as to cause the sensors to descend to the level of the cervical oesophagus, and the registration of UOS after-contraction is, therefore, an accurately recorded parameter and not, as has been suggested with a sleeve catheter side-hole similarly positioned, a reflection of the re-entry of the catheter into the sphincter (Kahrilas et al 1988a). The reasons for this are explained below.

The standard deviations of the Gaeltec and sleeve values (Table 4.7) show a wide range of relaxation pressures, particularly with the sleeve sensor. There is also a significant difference between the two catheters, with Gaeltec values being several mmHg higher than the sleeve side-hole or sensor values. The repeatability of relaxation pressure was, moreover, by far the worst of any parameter studied (CR = 0.96, Table 4.8). It is not surprising, therefore, that many reports do not quote relaxation pressures. Hellemans et al (1981) define relaxation as being 'at least to atmospheric pressure' while Rex et al (1988) report a greater degree of relaxation than in the present study (1.6 mmHg with their circumferential strain gauge) but with a similarly wide distribution about this point (SD = 2.9 mmHg).

Early studies reported a markedly negative UOS relaxation pressure (Fyke and Code 1955), ie to well below oesophageal baseline pressure, which is at a mean negative pressure relative to the pharynx over the respiratory cycle, although the possible contribution of movement artifact to these pressures has also been recognised for many years (Atkinson et al 1957). Some authors continue to report markedly negative pressures (-10 to -20 mmHg) in the UOS during normal relaxation (Mendelsohn et al 1987) while others define complete UOS relaxation as a fall to the level of intra-oesophageal pressure (Kahrilas et al 1986). The range of observed relaxation pressure in the present study was from -3.3 to 18.6 mmHg with the Gaeltec catheter, ie although pressures negative to intrapharyngeal zero reference were occasionally encountered, the residual relaxation value was positive in the majority of the 50 subjects. Differences in movement of the sphincter relative to the catheter are likely to explain these discrepancies and also the significant differences between the Gaeltec catheter and the sleeve sensor in the present study. Both have a more than adequate rate of recording of pressure fall (2000 mmHg/sec for the sleeve sensor, and several times greater than this for the intraluminal transducers) to track UOS relaxation accurately, as the total pressure fall was usually less than 100 mmHg. The finding of a greater residual relaxation pressure with the Gaeltec catheter points, therefore, to a smaller degree of sphincter-on-catheter movement on swallowing. One possible explanation for this is the presence of a greater degree of intranasal fixation with the broad sleeve catheter (maximum diameter 7.2 mm). Interestingly, Kahrilas et al (1986) observed similar UOS residual pressure following belch - rather than swallow-induced relaxations (3 to 9 mmHg) which was attributed to the residual tissue pressure in the absence of cricoid elevation. An alternative explanation is that this lack of movement prevented the recording of spurious negative relaxation pressures. As the surfaces of the nasal cavity are separated by about 4 mm, it is postulated that any catheter of diameter greater than 4 mm is liable to greater intranasal fixation than fine-bore type described here.

There is as yet no ideal method for the registration of UOS deglutition pressures. Strain gauge assemblies of the type used in the present study are extremely non-irritant and have a suitable frequency response but are liable to slip out of the UOS during swallow studies. Nor is the sleeve catheter ideal: the sideholes cannot accurately record pharyngeal pressure and the sleeve sensor must either be sited across the UOS, so that sphincter after-contraction is recorded prematurely when the pharyngeal contraction impinges on its inflow port, or, as in the present study, with its upper end within the high pressure zone when it too becomes liable to movement out of the UOS during laryngeal elevation. In either position, its slow rate of rise compromises accurate recording. What does emerge from the present study is that, despite an element of catheter movement, the UOS pressure usually does not fall to atmospheric or sub-atmospheric levels as has previously been thought.

4.5 THE EFFECT OF BOLUS CONSISTENCY ON PHARYNGO-OESOPHAGEAL MOTILITY

4.5.1 Methods

Following the series of UOS water swallows, the healthy volunteers described in 4.4.2 were each given four 5 ml swallows of a semi-solid mousse. The mousse was given by a teaspoon into the subject's mouth to prevent any head movement which might have influenced the positioning of the catheter. The subject who had double swallows of water and who experienced some associated discomfort was not included in this part of the study. After the mousse swallows, each subject was given a quarter slice of buttered bread and instructed to chew and swallow this in his or her usual manner.

The motility parameters measured for each substance were the duration and amplitude of pharyngeal contraction 3 cm above the maximum tonic UOS pressure; the duration and magnitude of UOS relaxation and after-contraction, the duration of the upper oesophageal wave 3 cm below the UOS recording level and the pharyngo-oesophageal wave velocity, measured over 11 cm from the peak of the pharyngeal contraction to the peak of the upper oesophageal wave 8 cm below the UOS recording level (Figure 4.3, Page 119, omitting Nos 2 and 3 which were used in the previous study to assess catheter response). The temporal pattern of UOS function was analysed twice for each subject. An initial measurement of UOS swallow complex duration was made from the peak of the 'E' wave (Section 4.4.7) to the endpoint of after-contraction. Data were later redisplayed and the interval of relaxation measured from the point of pressure fall below UOS baseline pressure to the point where baseline pressure was restored. The duration of UOS after-contraction from this point to the end of the pressure augmentation wave was also calculated. The UOS swallow complex duration was, therefore, greater than the sum of the relaxation and after-contraction intervals because it included the pressure fall from the peak of the 'E' wave. Double or multiple swallows were defined as swallows where the fall of the first after-contraction was continuous with the subsequent relaxation without an intervening period of baseline tonic UOS pressure. Where double swallows were present, the mean of the two pharyngeal peaks, UOS relaxations and after-contractions are reported, together with the total duration of the double UOS swallow complex. Data were analysed using the SPSSX programme by Student's paired t-test and by Spearman correlation coefficients (r_s).

4.5.2 Results

Single deglutition patterns were observed consistently in 21 subjects during mousse swallows and in 32 subjects during bread swallows (Table 4.9). Paired t-test comparison was performed to compare the results of the subjects who swallowed both water and mousse (21) and water and bread (32) in single events. The results show that UOS and pharyngeal contraction amplitudes were similar for mousse and water but that mousse was swallowed with a significantly greater mean relaxation pressure (11 mmHg) than water (7 mmHg, $p < 0.02$), whereas bread swallows were characterised by significantly greater contraction amplitudes in the pharynx and UOS (Figure 4.13). Both substances showed increased duration of the pharyngeal and upper oesophageal waves, and of the UOS swallow complex when the early 'E' wave fall was included in this measurement (Figure 4.14). Some of the difference in UOS swallow complex duration was shown to be due to a slight increase in the duration of UOS after-contraction with mousse and bread (Table 4.9) but, like the relaxation interval when recomputed to exclude the 'E' wave component, was not significant on a paired t-test. The velocity of the pharyngo-oesophageal wave was significantly reduced for both mousse ($p < 0.001$) and bread ($p < 0.005$) compared with water. T-test comparison of the males and females in each group showed no significant sex difference in any bread or mousse swallow parameter.

TABLE 4.9 - Normal Single Swallow Patterns of Water, Mousse and Bread

	WATER (n = 49)		MOUSSE (n = 21)			BREAD (n = 32)		(n = 49)
	MEAN	SD	MEAN	SD	r_s	MEAN	SD	r_s^{ϕ}
Pressure (mmHg)								
- peak pharynx	36	17	44	20	0.49*	46**	15	0.67***
- UOS minimum relaxation	7	5	11*	5	0.39^{+}	7	6	0.42***
- UOS after-contraction	76	24	85	23	0.34	95**	30	0.35^{++}
Duration (secs)								
- pharyngeal contraction	1.45	0.34	1.85^{++}	0.54	0.11	1.74***	0.45	0.66***
- UOS relaxation	1.27	0.40	1.27	0.29	0.25	1.30	0.38	0.58***
- UOS after-contraction	2.60	0.86	2.77	0.63	0.09	2.80	0.75	0.52***
- total UOS swallow complex	4.34	1.16	4.98*	1.47	0.62**	5.43***	1.97	0.60***
- upper oesophageal contraction	3.44	0.89	4.28^{++}	0.99	0.52*	4.31***	1.35	0.56***
Pharyngo-oesophageal motility (cm/sec)	3.10	0.58	2.40***	0.81	0.65**	2.63**	0.62	0.46***

$^{\phi}$ r_s for bread swallows includes 17 older volunteers

$^{+}$ $p < 0.05$, * $p < 0.02$, $^{++}$ $p < 0.01$, ** $p < 0.005$, *** $p < 0.001$ vs water swallows

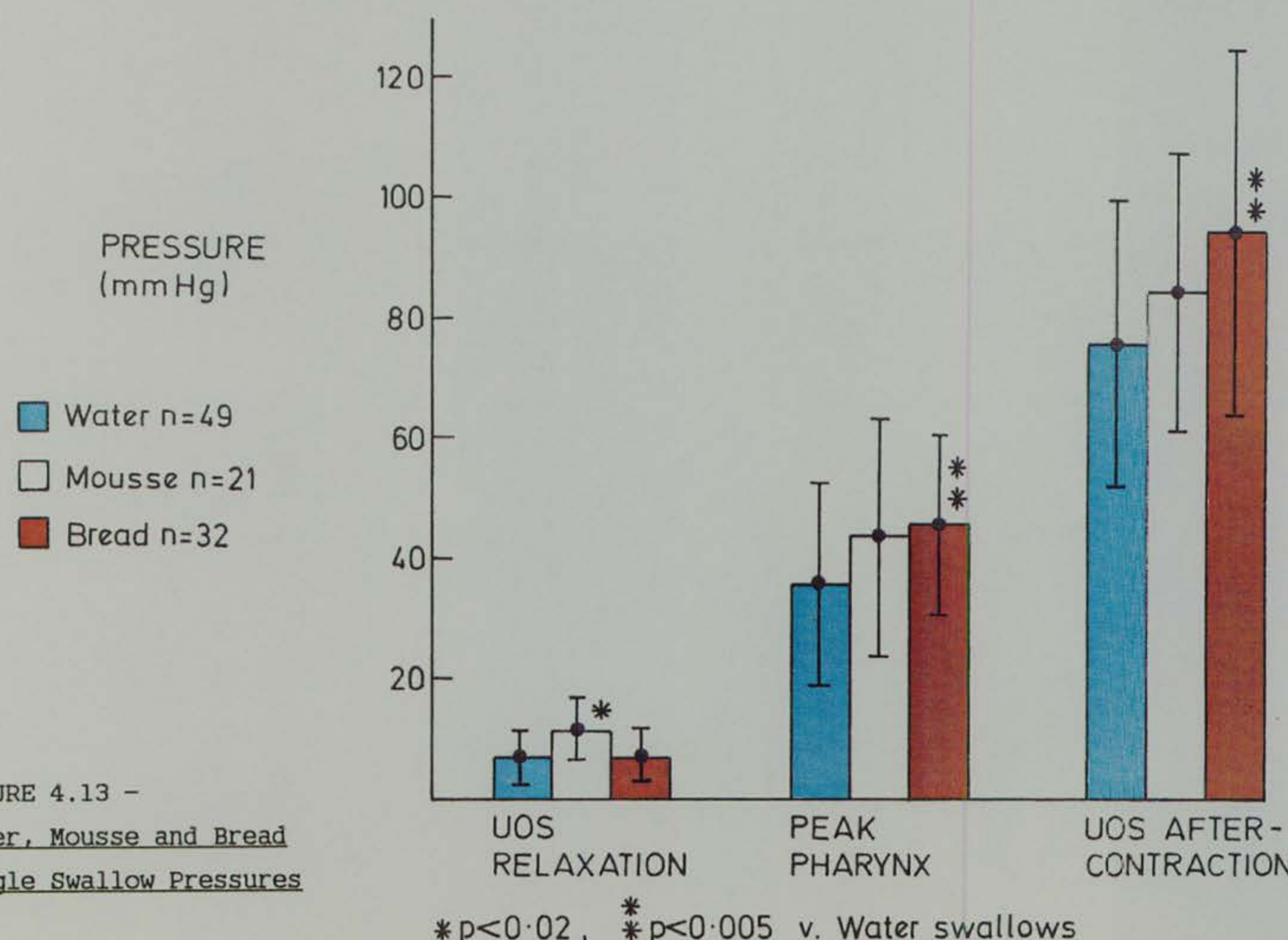
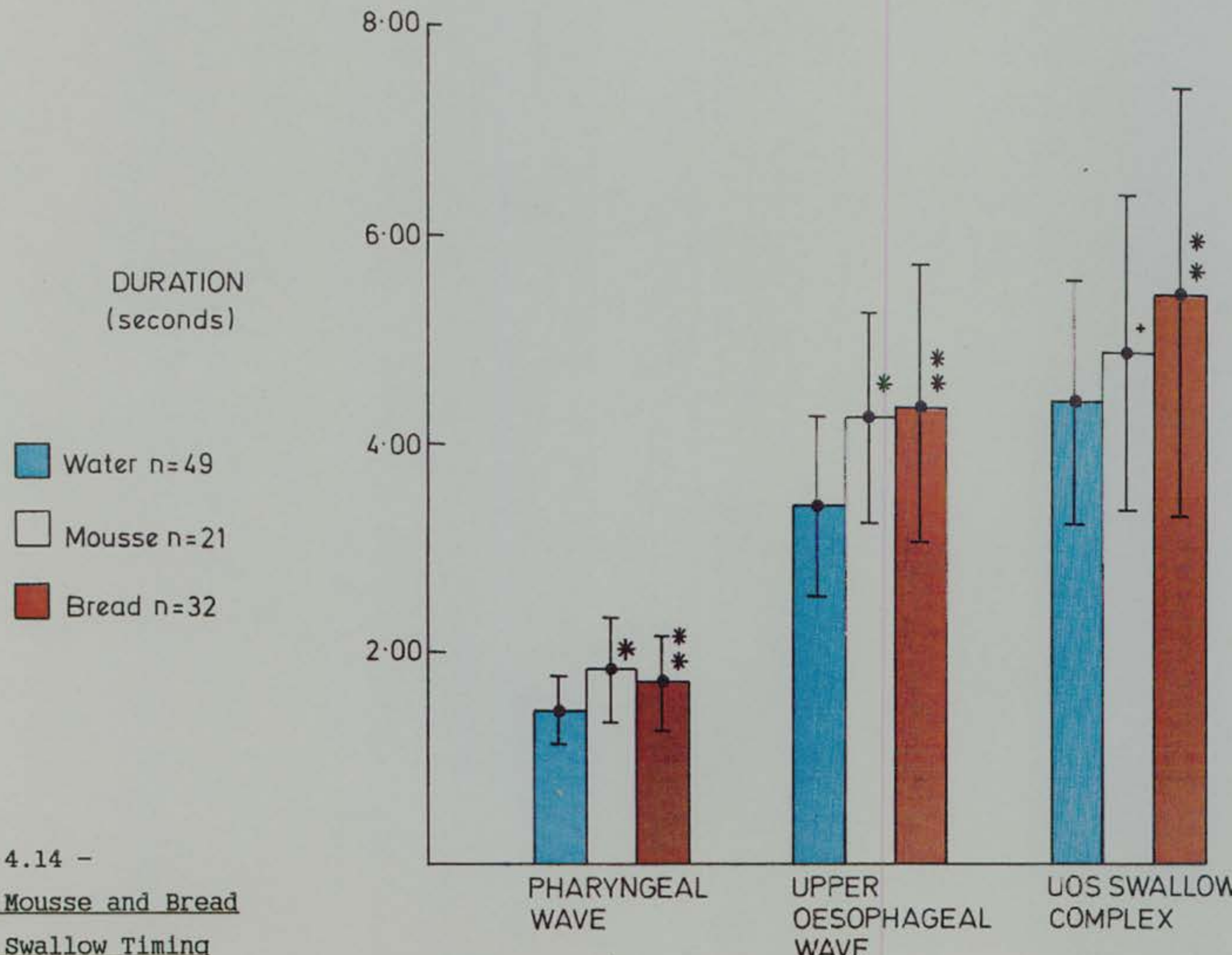


FIGURE 4.13 –

Water, Mousse and Bread Single Swallow Pressures



+p<0·02, *p<0·01, **p<0·001 v. Water swallows.

FIGURE 4.14 –

<u>Water, Mousse and Bread</u>

<u>Single Swallow Timing</u>

The correlation coefficients for single water and single bread swallow parameters (Table 4.9) were calculated in 49 volunteers - the 32 with single bread swallows in the present series and the 17 older subjects described in Section 4.6. In the smaller group of 21 subjects whose water and mousse swallow results were correlated, the greatest correlation coefficient of water and mousse swallow pressure was that of pharyngeal pressure ($r_s = 0.49$). The greatest correlation of bread and water swallow pressures was also that of the pharyngeal contraction amplitude ($r_s = 0.67$). Of the temporal mousse swallow parameters, only after-contraction and UOS swallow complex duration and pharyngo-oesophageal wave velocity were significantly associated with the corresponding water swallow pressure. In the 49 subjects whose single bread swallow results were analysed, all the durations measured and the wave velocity were significantly correlated with the water swallow values.

During single swallows (of either water or bread) the duration of the contraction waves in the pharynx, UOS and upper oesophagus were positively correlated ($p < 0.001$) and all were universally related to the pharyngo-oesophageal wave velocity. The height of the pharyngeal contraction was also inversely related to the duration of the pharyngeal contraction, but all of these relationships may have been influenced by the effect of age, which is considered in Section 4.6. Peak pharyngeal pressure coincided with minimum UOS relaxation pressure in 72% of water swallows, 58% of mousse swallows and 66% of bread swallows (NS).

In 14 of the 32 subjects with single bread swallows, mousse was also swallowed in single events. Paired t-test comparison of mousse and bread swallows in this group showed significantly greater after-contraction pressure with bread ($t = 2.6$, $p < 0.03$) and a trend to less complete UOS relaxation with mousse ($t = 2.1$, $p = 0.053$). The duration of the UOS mousse swallow complex was also significantly shorter than that of bread ($t = 2.3$, $p < 0.05$). Double swallow patterns were observed in 23 subjects for mousse and in 12 subjects for bread. Only six subjects showed double swallow patterns for both. There was no significant difference in the means of the pair of pharyngeal contractions (43 mmHg for mousse, 37 mmHg for bread) or of the pair of relaxation pressures (11 mmHg for mousse, 12 mmHg for bread). The length of the double swallow complex was also similar in both groups (8.33 sec for mousse, 8.26 sec for bread). UOS after-contraction was significantly greater for bread (102 mmHg) than mousse (90 mmHg) on a paired t-test of the six subjects with double swallows of both substances ($t = 2.7$, $p < 0.05$). The remaining subjects consistently swallowed mousse or bread in triple or quadruple complexes, during which an increased amplitude of UOS after-contraction in the last of the component swallows was frequently observed.

4.5.3 Discussion

For many years radiological studies of swallowing have included reports of the effect of bolus consistency on the mechanism of deglutition (Christrup 1964) because of the variable dysphagia for solids or liquids encountered in clinical practice. In the oesophageal body, it is known that 5 ml water swallows produce much more reliable motility patterns than do dry swallows, which show an increased incidence of double-peaked waves and non-peristaltic contractions. The advent of prolonged ambulatory manometric recording has also allowed oesophageal motility to be studied during eating (Howard et al 1988b) but there have been very few studies of the effects of bolus consistency on UOS manometry. Comparisons of UOS motility following dry and wet swallows were performed by Dodds et al (1975) using strain gauges, and by Kahrilas et al (1987a), using a sleeve catheter. Dodds' group reported no difference in the duration of UOS relaxation nor in pharyngeal peristalsis, whereas Kahrilas' results indicated an increase in the duration of UOS relaxation during wet swallows compared with dry swallows, but no other parameters were reported.

The present results show significant alterations in pharyngo-oesophageal kinetics during swallowing of different foods. Semi-solid (mousse), although given in discrete 5 ml boluses, was more often swallowed in double/multiple events than in single swallows. Single mousse swallows showed an incomplete UOS relaxation, comparable to that observed with double bread swallows, with a residual pressure of 10 mmHg relative to intrapharyngeal zero reference. The swallowing of bread, which was allowed to proceed in the subject's natural manner (given the constraint of the presence of the catheter) was most often in single events with high amplitude pharyngeal and UOS after-contraction amplitudes (Figure 4.13).

A recent detailed manofluorometric investigation of wet and dry swallow patterns in 26 healthy volunteers (Cerenko et al 1989) attempted to analyse the differences between the two types of swallow in terms of the force applied to the bolus, ie the area under the pressure curve (pressure x time in seconds). The authors define an oropharyngeal propulsion pump which is the sum of the 'transmitted tongue driving force' and the 'pharyngeal clearing force'. These forces are derived from two small pressure slopes preceding the pharyngeal contraction waves and are, in effect, equivalent to the 'slurring' phenomenon which precedes the peristaltic wave in the distal oesophagus and which is due to the passive transmission of pharyngeal pressures by the passing bolus. The two forces were, therefore, noted to be absent during dry swallows, ie in the absence of a bolus. Cerenko et al conclude that the subsequent peristaltic wave, which can be seen to occur after bolus passage during water swallows, subserves only a 'clearing' function to remove any residual fluid. This conclusion must be questioned on two counts. Firstly, if the same philosophy were extended to the oesophageal body, the important event in oesophageal peristalsis would also be the transmitted pharyngeal 'slur', as the oesophageal wave also occurs after the bolus has passed. Secondly, the findings of the present study indicate significant increases in the amplitude of the pharyngeal and UOS contraction waves during solid swallows. Thus, although it is quite possible that tongue propulsion is the major influence on pharyngeal bolus passage, and despite the fact that the pharyngeal and UOS pressure waves occur after the major part of the bolus has passed, the increase in amplitude of these contractions observed during bread swallows suggests that the pharyngo-oesophageal waves are indeed important in the normal swallowing act. In addition to the oropharyngeal propulsion pump, Cerenko's group also define a 'hypopharyngeal suction pump' on the basis of the markedly negative pressures recorded from the UOS during dry swallows. The period during which these negative pressures were recorded was markedly reduced during water swallows, a finding attributed to the contact of the bolus with the sensor causing an immediate increase in pressure to intrapharyngeal reference pressure or above. Differences in bolus properties may, therefore, explain the less marked UOS relaxation noted in the present study during mousse swallows. As has already been noted, however, (Section 4.4.7) markedly negative UOS relaxation pressures were the exception rather than the rule during the present series of investigations, and the effect of catheter movement, which may also have influenced the UOS relaxation results, was not considered by Cerenko et al. The finding of significant increases in pharyngeal and upper oesophageal pressures during bread swallows, in addition to an increase in UOS after-contraction amplitude, suggests that the observed alterations of the swallow pattern cannot be ascribed solely to differences in sphincter-on-catheter movement.

Both mousse and bread swallows showed significantly increased duration of the pharyngeal wave, upper oesophageal wave and UOS swallow complex when calculated to include the 'E' wave (Figure 4.14). Without this inclusion, however, the differences in UOS swallow complex duration would not have been significant, in view of the much smaller increases in the duration of the relaxation and after-contraction waves during bread and mousse swallows (Table 4.9). In other words, the pharyngeal and upper oesophageal waves are prolonged during swallows of solids or semisolids, but the major effect in the temporal pattern within the sphincter was on the duration of the elevation wave which preceded UOS relaxation. Lund (1965b) emphasised the distinction between UOS relaxation and the opening of the sphincter, and observed that a greater degree of cricoid movement is necessary to open the sphincter in the presence of a larger bolus. Cook et al (1988b) also showed that increases in bolus volume cause a progressively earlier onset of anterior hyoid and laryngeal movement and it is possible that changes in bolus consistency may provoke similar changes. Lingual peristalsis has also been shown to be more forceful with more solid boluses (Shaker et al 1988a). Cook et al (1988a) also showed progressive increase in trans-sphincter flow with increase in the volume of barium swallowed, in a manofluorometric study of eight healthy volunteers. In the present study the velocity of the pharyngo-oesophageal pressure wave was significantly reduced for both mousse and bread compared with water swallows, although it is not known whether there was a concomitant reduction in bolus velocity.

There has been one previous preliminary report of the effect of swallowing different foods on UOS motility by Castell et al (1988) who studied 5 ml swallows of water and of apple sauce and swallows of 1/8th marshmallow in 10 subjects. An on-line computer was used to derive 15 temporal parameters. No significant alteration in pharyngeal contraction amplitude or duration was observed with different foods, unlike the present study where both were increased for bread, and duration also for mousse. The discrepancy is perhaps due to the nature of the food used (1/8th marshmallow vs bread eaten ad libitum) and to the small number of subjects studied. As in the present study, there was less complete UOS relaxation with semisolid than solid swallows, and semisolid swallows also showed least coordination of the pharyngeal peak with the nadir of UOS relaxation. In the present study, the number of swallows where the maximum pharyngeal pressure coincided with UOS minimum pressure was scored (72% for water vs

58% for mousse) but in view of the possible importance of UOS pressure at the moment of peak pharyngeal contraction, it was decided to calculate the value of this pressure in future studies.

More than half of the subjects in this study swallowed 5 ml mousse boluses in double or multiple complexes. It is possible that a tenacious residue of mousse provoked a second swallow, or that the presence of the catheter leads to an increased incidence of double swallows. The high incidence of mousse double swallows may limit the usefulness of this type of semisolid in comparative studies of controls and patients as these complexes are harder to analyse than single swallows because of the greater associated catheter movement. It appears that for bread but not for mousse, the presence of a double swallow is associated with less complete UOS relaxation (12 mmHg) than is a single swallow (7 mmHg). The incidence of multiple swallows during eating in the absence of a catheter is, of course, unknown but the early results of ambulatory motility studies indicate that reduced inter-swallow interval, with secondary deglutitive inhibition, may contribute to the development of non-conducted swallows, aperistalsis and symptomatic dysphagia in patients with GOR (Howard et al 1988b).

The observed alterations in pharyngo-oesophageal kinetics are important for several reasons. The results support peripheral sensory feedback mechanisms in the generation of motility patterns. This conclusion is supported by the recent manofluorometric studies which show alterations in the magnitude and the duration of UOS opening during swallows of increasing volumes of barium (Cook et al 1988a, Kahrilas et al 1988a). The apparent dependency on sensory feedback of the swallow response is also, of course, in keeping with the wellrecognised difficulty in the performance of more than four to six dry swallows (Magendie 1823). The correlation coefficients of the water swallow pressure and timing parameters with the corresponding bread swallow parameters in 49 subjects were, however, all highly significant (Table 4.9) which suggests that the pattern of deglutition in a given subject is, to some extent at least, 'pre-set'. This concept is further explored in Section 4.6 in relation to the effect of subject variables such as age and sex on motility patterns.

The present results establish useful normal ranges of pharyngo-oesophageal motility for use in future studies of patients with a greater degree of dysphagia for certain types of food, in whom an abnormality might be overlooked if only water swallow studies were performed. In this respect, the very fine-bore Gaeltec assembly is likely to induce the minimum possible artifact. The use of an automated analysis (Castell et al 1988), where available, would also appear to be particularly advantageous in this situation because the number of swallows studied in each subject is rendered very much greater. More important is the nature of the food ingested; it is not surprising that the swallowing of a mouthful of bread produces more marked changes in pharyngo-oesophageal motility than the swallowing of a tiny cube of marshmallow. The calculation of 15 temporal parameters by Castell's group is of interest in that it is likely to lead to the identification of the most important discriminants of abnormal motility but it is inappropriate outwith a research context, not only because of the current lack of availability of automated analysis but also because it it unlikely that an abnormality in only one or two of 15 such parameters will be of clinical significance.

4.6 THE EFFECT OF AGE, SEX AND CIGARETTE SMOKING ON PHARYNGO-OESOPHAGEAL MOTILITY

The studies described in Section 4.4 and Section 4.5 have characterised normal pharyngo-oesophageal motility in young and middle-aged subjects, but many of the patients presenting with disorders of UOS motility are considerably older. The aim of this study was to establish the effects of ageing on normal pharyngo-oesophageal motility by the study of an older cohort of asymptomatic volunteers. Possible associations with sex or cigarette smoking were also explored, in view of the different incidence in males and females of conditions such as globus pharyngis and pharyngeal pouch, and because of the planned study of patients following treatment for laryngeal carcinoma. Previous sections of this chapter have been concerned with the influence of recording system variables on UOS motility, but the optimum method of scoring UOS tonic pressure has not been so far considered. A comparison was made in this study of UOS RPT and SPT parameters in over 100 controls and patients.

4.6.1 <u>Methods</u>

Seventeen additional volunteers, 11 males and six females, aged 60 to 77 years, were recruited from the ENT outpatient department. Some were patients attending the clinic to obtain a hearing aid, for mastoid cavity toilet or with otitis externa; the rest were accompanying friends or relatives who responded to notices placed in the waiting areas. None had a history of dysphagia, globus, previous radiotherapy or of neurological or other disease liable to influence deglutition. In view of the age of the subjects, it was decided to minimise the duration of the investigation by using only the strain gauge assembly and by omitting the mousse swallow studies. The study protocol was otherwise as described in Section 4.2.2 and Section 4.5.1 but with the addition of RPT measurement of UOS tonic pressure, and of timing of the UOS SPT to give exactly 20 sec at each 0.5 cm station. The mean pressure obtained during three RPTs at 1 cm/sec during quiet respiration from five or six strain gauges was calculated. The maximum tonic and average tonic SPT pressures (Figure 4.1b, Page 90, Nos 2 and 3) were also calculated. It is not known whether the greatest maximum pressure in a single radial orientation is also an important determinant of UOS barrier function and the maximum tonic pressure in any single channel was, therefore, also calculated. The reporting of tonic pressures in this way does not, however, take any account of the length over which they are distributed, which was suggested by Pope (1967) to be an important factor in sphincter strength. The index of the mean tonic pressure during the timed SPT divided by the observed sphincter length was, therefore, calculated and expressed in mmHg/cm. RPT data were also available for eight of the younger volunteers. To assess pharyngo-oesophageal coordination more precisely, the mean pressure in the three UOS strain gauges at the moment of peak pharyngeal pressure was measured for water and bread swallows.

The combined data obtained from the original 50 control subjects, four of whom were aged over 60 years (Section 4.4.2) and from the additional group of 17 older controls were analysed using the SPSSX programme by Spearmen rank correlation to assess the effects of age and by unpaired Student's t-test to assess the effects, if any, of sex and cigarette smoking.

The UOS tonic pressure parameters measured in the controls, and in a group of 98 patients investigated during the studies reported in Chapter 6 and Chapter 7, were compared by paired Student's t-test and by rank correlation. A further analysis of the effect of age and sex on pharyngo-oesophageal motility was made in a combined group of 185 subjects, comprising the 67 volunteers plus 118 patients with globus sensation, functional cervical dysphagia or neurological cervical dysphagia, using regression analysis to exclude any differences due to the diagnostic group.

4.6.2 Results

The age of the total group of 39 male volunteers (40 $\pm$ 20 years) was not significantly different from that of the 28 females (43 $\pm$ 17 years). There was no significant relationship of age with tonic LOS pressure but there was a positive association of age with sphincter length ($r_s = 0.42$, $p < 0.001$). Peristaltic amplitude was inversely associated with age ($r_s = -0.45$, $p < 0.001$). Mean amplitude was 81 mmHg in 15 subjects aged under 25 years; 93 mmHg in the 21 aged 26 to 35 years and 88 mmHg in the 10 aged 36 to 56 years. The mean pressure fell to 52 mmHg in the 11 aged 60 to 65 years, with a further decrease to 42 mmHg in the 10 aged 65 to 77 years. Parameters showing significant differences between those under 57 years of age and those aged between 60 and 77 years are listed in Table 4.10. Peristaltic velocity was similar in those under 57 years (3.06 $\pm$ 0.61 cm/sec) and in those over 59 years (3.29 $\pm$ 1.01 cm/sec, NS).

Tonic UOS pressure was significantly lower in the subjects aged over 59 years (Table 4.10) and the correlation of age with maximum tonic UOS pressure confirmed this inverse relationship ($r_s = -0.21$, $p < 0.05$). This fall was independent of the concomitant fall in peristaltic pressure on regression analysis of the three variables. During motility studies of swallowing, the most marked pressure difference was in pharyngeal contraction amplitude which showed a positive association with age ($r_s = 0.37$ for water; $r_s = 0.50$ for bread, both $p < 0.001$), ie the opposite age-association to that observed for peristaltic amplitude in the distal oesophagus. There was a trend to an associated reduction in the duration of pharyngeal wave but the reduction in upper oesophageal wave duration was even more marked. During bread swallows only, there was also a significant reduction in the duration of UOS after-contraction ($r_s = 0.41$, $p < 0.002$) and an increase in pharyngo-oesophageal wave velocity .

TABLE 4.10 - Principal Age-Related Alterations in Normal Manometry

	AGE < 57 YEARS (n = 46) MEAN	SD	AGE > 59 YEARS (n = 21) MEAN	SD	r_s (with age)
Pressure (mmHg)					
Peristaltic contraction	89	40	49**	32	-0.45**
UOS maximum tonic	40	15	32$^+$	14	-0.21$^+$
Water swallow					
- pharyngeal	36	16	71**	35	0.37**
- UOS after-contraction	78	27	100$^{\emptyset}$	52	0.12
Bread swallow					
- pharyngeal	45	19	86**	43	0.50**
- UOS after-contraction	99	30	107	37	0.10
Duration (sec)					
Water swallow					
- pharynx	1.47	0.35	1.23$^{\emptyset}$	0.59	-0.20$^{\emptyset}$
- upper oesophagus	3.48	0.92	2.49**	0.73	-0.54**
Bread swallow					
- pharynx	1.71	0.43	1.33$^{\emptyset}$	0.89	-0.38^{++}
- upper oesophagus	4.41	1.39	2.83**	0.88	-0.62**
Pharyngo-oesophageal wave velocity (cm/sec)					
- water	3.11	0.60	3.34	0.87	0.08
- bread	2.60	0.62	3.18*	1.10	0.31*

$^{\emptyset}$ $0.1 > p > 0.05$, $^+$ $p < 0.05$, * $p < 0.02$, $^{++}$ $p < 0.005$, ** $p < 0.001$

The residual UOS pressure at the moment of peak pharyngeal contraction was 10.0 ± 5 mmHg for single water swallows and 12.4 ± 7.3 mmHg for single bread swallows in the 17 controls in whom this parameter was measured. In a total of 45 patients and controls in whom this parameter was measured and who had single swallows for both substances, the mean UOS pressure at peak pharyngeal contraction was 9.2 ± 7.2 mmHg during water swallows and 14.0 ± 13.3 mmHg during bread swallows ($p < 0.02$), with corresponding minimum relaxation pressures of 5.9 ± 6.5 mmHg for water and 4.7 ± 9.4 mmHg for bread swallows (NS). The minimum relaxation pressure preceded the pharyngeal peak in almost all subjects.

T-test comparison of each of the lower and upper oesophageal parameters in the 39 male with the 28 female volunteers showed a significant difference in only one - UOS water swallow after-contraction pressure. There was also a somewhat greater mean distal peristaltic amplitude in females (85 ± 44 mmHg) than in males (69 ± 35 mmHg) but the difference was not significant. The increase in UOS after-contraction in females was very much greater, with the mean pressure in females (98 ± 46 mmHg) being more than 20 mmHg greater than that in males (76 ± 28 mmHg, $t = 2.2$, $p < 0.05$). Bread swallow UOS after-contraction pressure was similar in males (103 ± 36 mmHg) and females (100 ± 27 mmHg). Thus, the mean increment between water and bread swallows in UOS after-contraction in males (27 mmHg) was considerably greater than that in females (2 mmHg, $t = 2.65$, $p = 0.01$).

Forty of the 67 controls were nonsmokers. The mean age of the smokers (34 ± 15 years) was significantly less than that of the nonsmokers (47 ± 19 years, $t = 3.04$, $p < 0.005$). Comparison of manometric results in the two groups showed a significant difference only in pharyngeal contraction amplitude which was significantly greater in nonsmokers (64 mmHg) than in smokers (48 mmHg, $t = 2.1$, $p < 0.05$). Regression analysis confirmed that this was due to the effect of age ($t = 5.3$, $p < 0.0001$) and not to the effect of cigarette smoking ($t = -0.8$, $p = 0.4$).

The different parameters of tonic UOS pressure obtained in the volunteers are listed in Table 4.11, together with the comparable findings in a larger group of patients. There was no significant difference between the mean of the RPT pressure peaks and the mean maximum tonic UOS pressure in either controls or patients. The maximum tonic pressure was approximately 15 mmHg greater, as expected in view of the demonstrated UOS radial asymmetry. Mean tonic pressure was only 17 mmHg when averaged over sphincter length, giving a pressure/length index of 5 mmHg/cm. The correlation coefficients indicate a greater degree of concordance among the SPT pressures than between RPT and maximum tonic sphincter pressure (Figure 4.15 and Figure 4.16).

Multiple regression of manometric findings in the total group of 185 controls analysed with age, sex and diagnostic group essentially confirmed the age and sex associations demonstrated in the smaller control group. The increase in peristaltic amplitude in females in this larger series of subjects was clearly significant ($t = 3.8$, $p < 0.001$). There was also an increase in distal peristaltic wave duration (but not velocity) with age ($t = 2.2$, $p < 0.05$). This was much less marked than the reduction in wet swallow wave duration in the upper oesophagus ($t = -3.2$, $p < 0.002$). There was no significant inter-relationship of peristaltic amplitude, duration or velocity in the 72 subjects in whom these parameters were measured. The reduction in tonic UOS pressure with age was confirmed, both for mean maximum tonic UOS pressure ($t = -2.6$, $p < 0.01$) and for the greatest maximum tonic pressure recorded from any one channel ($t = -3.0$, $p < 0.005$). Regression of wet swallow UOS after-contraction pressure showed a weak increase with age ($t = 2.03$, $p < 0.05$) but a greater increase in females compared with males ($t = 2.6$, $p < 0.01$).

TABLE 4.11 - Comparison of Methods of UOS Tonic Pressure Measurement

	VOLUNTEERS			PATIENTS			
UOS Pressure (mmHg)	n	MEAN	SD	n	MEAN	SD	r_s ø
Mean of 3 RPTs	25	35	14	98	37	15	0.72
Mean maximum tonic SPT	67	37	15	118	36	17	--
Maximum tonic SPT	17	51	27	98	59	32	0.90
Mean tonic SPT	17	17	6	88	18	8	0.88
Mean pressure/cm	17	5	2	88	5	3	0.73

ø correlation with mean maximum tonic pressure in the combined group of volunteers and patients, all $p < 0.001$

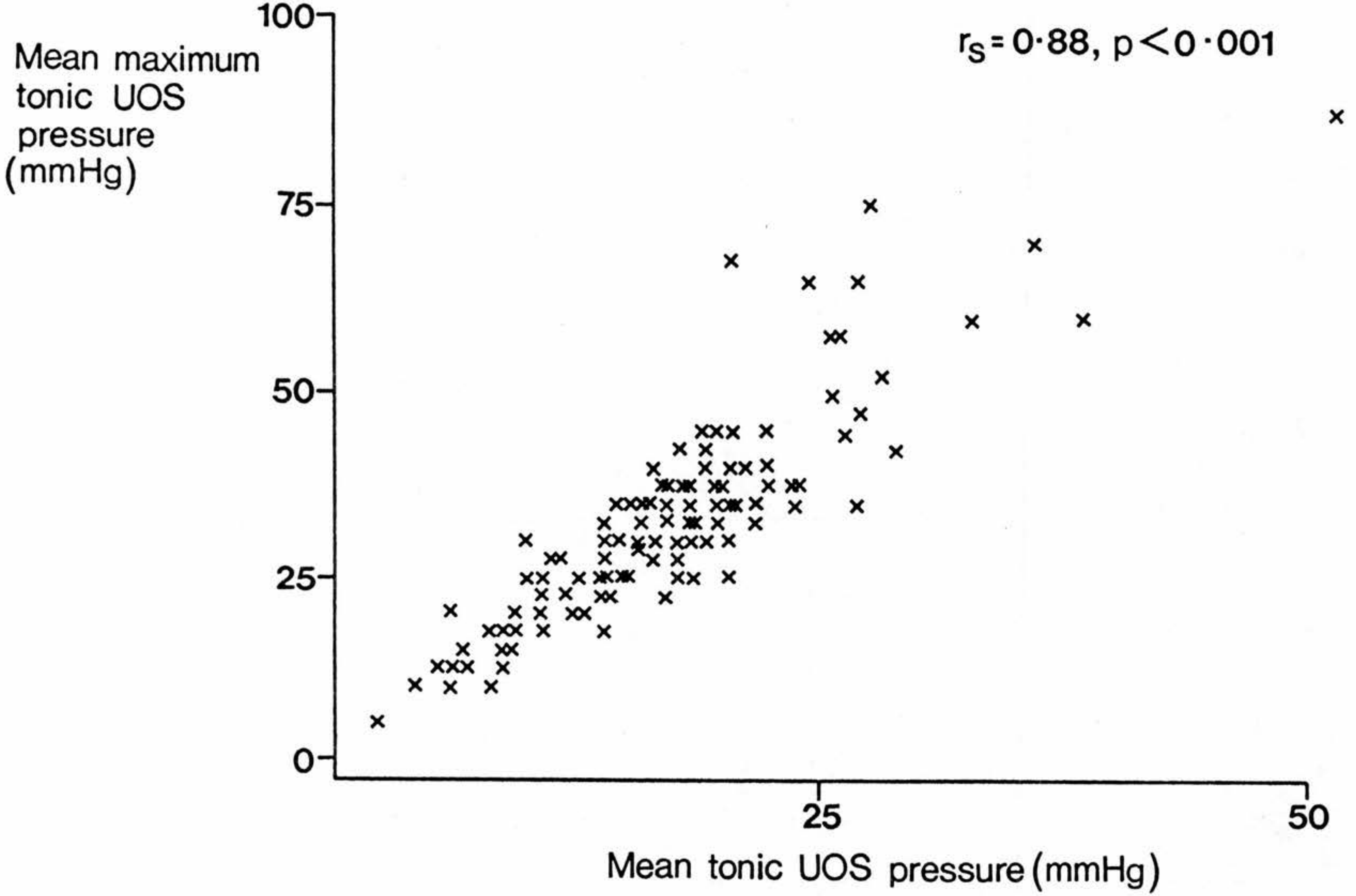


FIGURE 4.15 - Plot of Mean Maximum Tonic UOS Pressure with Mean Tonic UOS Pressure (n = 105)

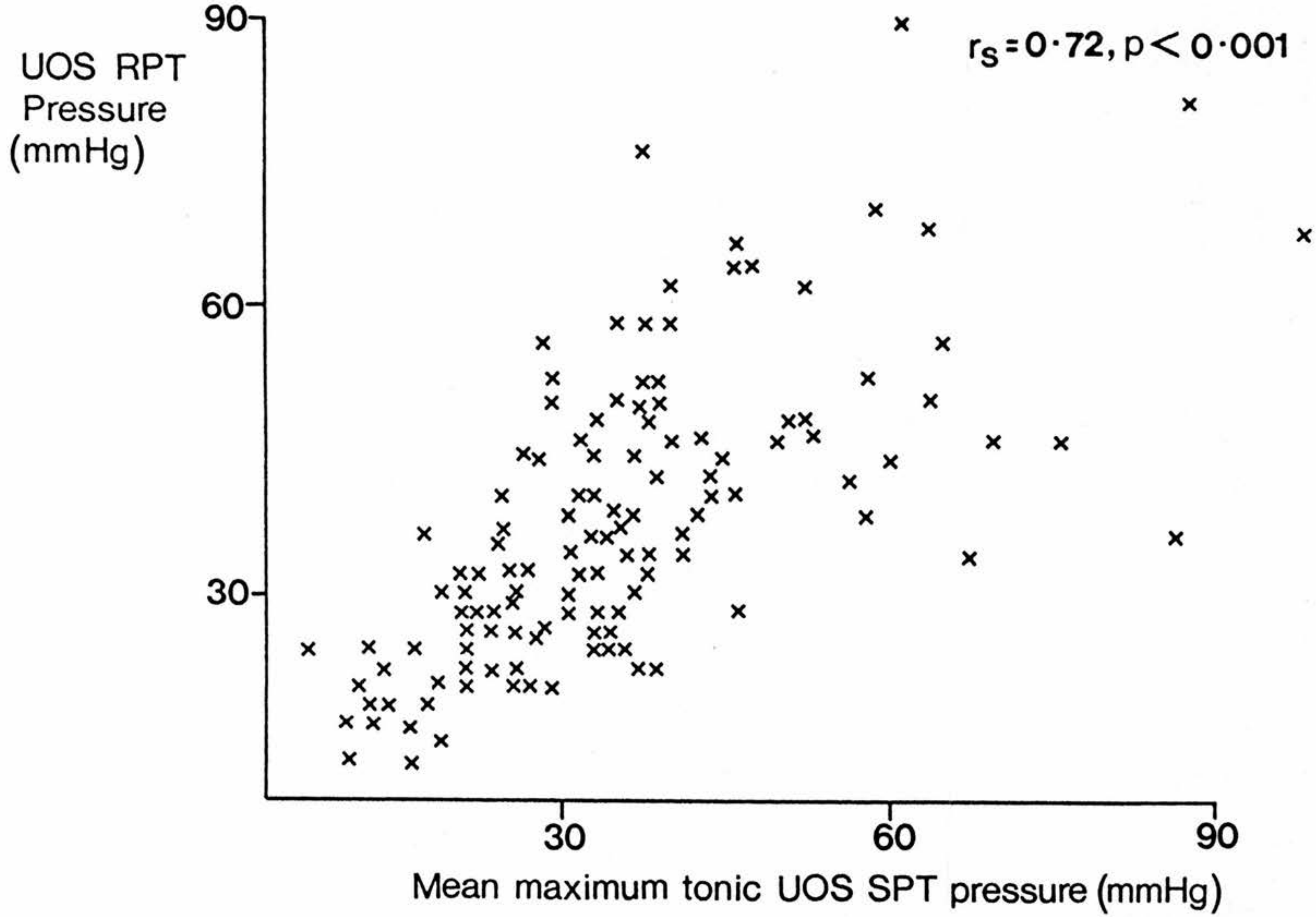


FIGURE 4.16 - Plot of UOS RPT Pressure with Maximum Tonic SPT Pressure (n = 123)

4.6.3 Discussion

This is the most detailed study to date of the effects of ageing on pharyngo-oesophageal motility. There have, however, been several reports of age-related changes in lower oesophageal manometry. The first of these (Soergel et al 1964) was a study of oesophageal motility in 15 nonagenarians using an early, water-filled catheter. In this older group, mean peristaltic amplitude was even lower (29 mmHg) than in the volunteers aged over 59 years in the present study (49 mmHg, Table 4.10), as might be expected in view of the strong age-association of peristaltic amplitude. The mean velocity of oesophageal peristalsis in Soergel's series of elderly patients (3.5 cm/sec) was similar to that in both the younger volunteers (3.1 cm/sec) and the older volunteers (3.3 cm/sec) in the present study, where no significant relationship of age and peristaltic velocity was demonstrated ($r_s = -0.04$). Ali Khan et al (1977) used a perfused catheter with a rapid infusion rate to compare lower oesophageal manometric findings in 43 normal subjects aged under 60 years with those in 49 subjects aged 60 to 89 years. LOS pressures were similar in the two groups, as in the present study. Peristaltic amplitude was again significantly lower in the older subjects who also had a significant reduction in peristaltic velocity (mean = 2.6 cm/sec) compared with the younger volunteers (mean = 3.3 cm/sec). Hollis and Castell (1974) used a 5 mm diameter intraluminal strain gauge to study a group of 21 males aged 70 to 87 years and found no alteration in peristaltic velocity or duration compared with younger subjects. Peristaltic amplitude was again significantly lower in the older controls, leading the authors to postulate that the age-related changes in distal oesophageal motility were due to a weakness of the smooth muscle in the presence of normal vagal innervation. A more recent report from the same centre (Richter et al 1987) did, however, show a reduction in duration as well as in amplitude of peristaltic contraction in the study of 95 volunteers to which previous reference has been made, although the relatively poor correlation of pressure with duration suggested to the authors that changes in neurohormonal control might accompany the reduction in smooth muscle contraction force in older subjects. In the present study, distal peristaltic wave duration was somewhat increased with increasing age in the combined group of volunteers and patients analysed by multiple regression, but there was a much more marked reduction in upper oesophageal wave duration. There were also no clear inter-relationships between distal peristaltic amplitude, duration and velocity. There was no significant sex difference in peristaltic amplitude in Richter's study but the present results indicated an (insignificant) increase in distal amplitude in female volunteers. On regression analysis of the larger group of patients and controls, the difference was, however, highly significant, but there has been no other report of a sex difference in peristaltic pressure. It is of particular interest because of the associated significantly greater wet swallow UOS contraction amplitude which was also present in female volunteers and patients.

The striated musculature of the pharynx has been shown in the present study (also it is believed for the first time) to exhibit significantly increased contractions of significantly reduced duration with increasing age. The fact that this pattern was present during both water and bread swallows confirms the validity of the observations, although the age-difference was more marked during bread swallows. The presence of a neural alteration in the pharynx may also be inferred since the contractions present in the upper oesophagus were also of reduced duration and, for bread swallows, the pharyngo-oesophageal wave velocity was significantly greater. The duration of the upper oesophageal wave is more than twice that of the duration of the pharyngeal wave and the greater absolute reduction in duration of the upper oesophageal wave compared with the pharyngeal wave is, therefore, likely to account for the inverse relationship of wave duration and pharyngo-oesophageal velocity. The reduction in duration of UOS after-contraction with age was significant only for bread swallows but the age-association of wave durations in the pharyngo-oesophageal segment is likely to make a major contribution to their inter-relationships (Section 4.5).

UOS after-contraction amplitude is different from pharyngeal contraction amplitude in having no significant age-association in healthy subjects (Table 4.10) and only a weak increase with age on regression analysis of over 180 volunteers and patients. There are two possible reasons for this. The first is the influence of sex, which was a more powerful variable than age in the regression equation, with females having significantly greater pressures. The second is the observed lower tonic UOS pressure in older subjects which might also be expected to alter UOS after-contraction pressure. Nonetheless, the duration of UOS after-contraction correlates well with the pharyngeal and oesophageal wave durations ($p < 0.001$, Section 4.5.2) and, during bread swallows, is inversely associated with increasing age. It would, therefore, be erroneous to conclude that the cricopharyngeus has different age-responses from the rest of the striated musculature of the pharynx on the basis of the present data. What is certain is that with increasing age in healthy volunteers there is an increase in peak pharyngeal pressure and a reduction in oesophageal body peristaltic pressure. The increase in pharyngeal pressure accompanies a reduction in UOS tone, and might represent a compensatory mechanism for airway protection. A similar theory is proposed to explain the increase in pharyngeal wave duration in the presence of UOS hypotonicity in patients with choking episodes (Section 7.2). The reason for the increased wet swallow UOS after-contraction in females is unclear, particularly as both sexes appear to exhibit similar UOS contraction pressures during bread swallows. The finding may, however, be relevant to the observed sex incidence of globus pharyngis, and is further considered in Section 6.4.

The results indicate (Table 4.11) that the difference between RPT and SPT measurements of UOS pressure, when averaged from five radially-disposed strain gauges, yield much more similar results than in the LOS (Table 4.4a, Page 122). This is a further reflection of the fact that LOS pressure measurement is, because of its diaphragmatic location, much more susceptible to respiratory variation, whereas in the UOS the major influences on measured tonic pressures are the diameter and radial sampling properties of the recording catheter particularly if, as in the present study, both RPT and SPT UOS measurements are made during quiet respiration. The finding of a pressure/length index of only 5 mmHg is due to the much greater total length of the high pressure zone than the 1 cm zone of greatest sustained pressure (Kahrilas et al 1988a). The previous studies of UOS RPT recording have all been performed using catheters which were of a diameter several millimetres broader than the 2.8 mm Gaeltic assembly with correspondingly greater measured pressures of over 100 mmHg (Weihrauch et al 1980b, Kahrilas et al 1987a, Rex et al 1988). Rex et al compared RPT and SPT measurements with both a radially and a circumferentially sensitve strain gauge and found RPT pressures to be 24 to 43 mmHg greater by each method. Kahrilas' RPT and SPT pressures were less comparable as the RPTs were performed with multilumen oval or round catheters while the SPT was with a sleeve catheter, but again the RPT pressures were sigificantly greater, unlike the present study where the RPT and SPT measurements of greatest tonic pressure were almost identical. This may be due to the lesser degree of UOS irritation caused by performing the RPT with a very fine-bore catheter. All the measurements of UOS pressure were so well-correlated (Table 4.11 and Figure 4.15) that the calculation of pressures other than the mean maximum tonic pressure may be unnecessary. Where a fine-bore catheter is not available, however, investigators should be aware of possible artifactual increases in pressure when using a continuous pull-through method.

It is also apparent from the present results that the minimum UOS relaxation pressure usually precedes the peak of the pharyngeal contraction. UOS pressure at the time of the pharyngeal peak is likely to prove a more valid parameter of pharyngo-oesophageal coordination than the minimum UOS pressure recorded, which shows no difference between water swallows and bread swallows and which may be more susceptible to movement artifact.

5. THE UPPER OESOPHAGEAL SPHINCTER AND GASTRO-OESOPHAGEAL REFLUX

Following the suggestion that GOR might cause a reflex increase in UOS tone (Hunt et al 1970) there have been several studies on the association of oesophageal acid exposure with UOS function. The conflicting results of these reports reflect the technical problems of UOS manometry, differences in the definition of oesophageal acid exposure and the small number of subjects studied. There have also been several reports linking GOR to posterior laryngeal inflammation, which have been discussed in Section 3.2. The aims of the studies described in this chapter were (a) to compare UOS function with the magnitude of GOR as assessed by prolonged ambulatory pH monitoring in a large number of subjects, (b) to determine the effect of acute upper oesophageal acid exposure on UOS tonic pressure and (c) to compare the results of prolonged monitoring of intraoesophageal pH with the posterior laryngeal biopsy findings in patients with laryngopharyngeal symptoms.

5.1 THE ASSOCIATION OF GASTRO-OESOPHAGEAL REFLUX AND UPPER OESOPHAGEAL SPHINCTER FUNCTION

5.1.1 Methods

Two manometric catheters were used in this study. Initial studies were performed using a conventional 8-channel perfused catheter (Arndorfer ESM3) which was linked to a capillary infusion pump and to a chart recorder (described in Section 4.1.2). Later, when the Gaeltec intraluminal strain-gauge assembly became available, this was used in conjunction with the GR800 recorder. The manometric protocol for the two catheters was as described in Section 4.1.2 and Section 4.3.1.

All subjects underwent 23 hour ambulatory pH monitoring, mostly on an outpatient basis. A Radiometer glass/KCl electrode with an integral reference electrode (V A Howe) was sited 3 cm above the manometric proximal LOS margin, and was attached to a digital pH meter (Synectics) strapped to the subject's waist. Subjects kept a diary card of all substances ingested, cigarettes smoked, times of recumbency and symptoms experienced. Diet and cigarette smoking were unrestricted.

5.1.2 Subjects and Data Analysis

The Arndorfer catheter was used to study 13 asymptomatic volunteer controls, mean age 27 years (SD = 4) and 85 patients with cervical symptoms, mean age 50 years (SD = 13). In 60 patients the principal complaint was of globus sensation. The remainder had dysphonia, alone or in combination with globus, burning pharyngeal discomfort or nocturnal cough. The Gaeltec catheter was used to study 25 patients, mean age 54 years (SD = 13). Seven of these had daily epigastric pain or heartburn; the remainder had laryngopharyngeal symptoms similar to those of the Arndorfer group.

Data were analysed using the SPSSX programme, by unpaired Student's t-test and Pearson correlation coefficients. Because of the age differences between patients and controls, manometric parameters were also subjected to multiple regression analysis.

5.1.3 Results

Total time of pH less than 4 (AET) was 2.1 to 6.5% (median 4.1%) in controls, 0.2 to 32.1% (median 4.9%) in patients with cervical symptoms and 0.3 to 36.4% (median 5.1%) in patients with dyspepsia. (Details of pH parameters in patients with cervical symptoms are discussed in Section 5.3 and Section 6.3). There was no association of AET with age or weight. Total AET was greater than 10% in 25 of the Arndorfer group and in seven of those studied with the Gaeltec catheter.

Manometric results are listed in Table 5.1 which includes a list

TABLE 5.1 - Manometric Findings (pressures in mmHg)

	ARNDORFER				GAELTEC			
	Controls (n = 13)		Patients (n = 85)		Controls (n = 67)		Patients (n = 25)	
	X	SD	X	SD	X	SD	X	SD
Age	27	14	50	13	42	19	54	13
LOS RPT								
- mean Pressure	30	16	32	15	19	9	25	11
UOS SPT								
- maximum tonic pressure	69	19	71	28	37	15	38	17
- peak (dry swallow pressure)	127	32	127	33	115	32	116	46
Wet Swallow								
- UOS after-contraction	107	29	130	58	85	38	106	46
- pharyngeal pressure	53	21	57	24	47	29	82	56
- duration (secs)	3.8	0.8	3.7	1.1	4.34	1.16	3.5	1.1

of the Gaeltec catheter findings in 67 healthy controls described in Section 4.4 and Section 4.6. In the patients studied with the Arndorfer catheter, LOS pressures were not significantly different between controls and patients with cervical symptoms. Regression analysis also showed no significant association of age or AET with LOS pressure. Mean Arndorfer UOS SPT peak and tonic pressures were also similar in patients and controls. As expected, with the exception of mean pharyngeal pressure, Gaeltec catheter pressures were all significantly lower than Arndorfer catheter measurements (see Section 4.2).

There was no significant correlation of AET with Arndorfer maximum tonic UOS pressure ($r = -0.18$), Figure 5.1, but tonic UOS pressure was inversely associated with age ($r = -0.28$, $p < 0.002$). On regression analysis of AET, group and age with tonic UOS pressure, only the reduction in UOS pressure with increasing age was significant ($t = 2.65$, $p < 0.01$). Although correlation of AET with peak UOS SPT pressure showed a weak inverse relationship of the two variables (Figure 5.2), regression analysis showed no significant association of peak pressure with group or AET. As with tonic UOS pressure, there was a trend to reduced peak pressure with increasing age ($t = 1.83$, $p = 0.07$). In the patients studied with the Gaeltec catheter, mean maximum tonic UOS pressure (38 mmHg) was almost identical to that in the control group (37 mmHg). There was again no significant association of AET and tonic UOS pressure ($r = 0.16$). In the 25 patients who were studied with the Arndorfer catheter and whose total AETs were greater than 10%, mean maximum tonic UOS pressure (62 mmHg) was slightly lower than that in the remaining 73 subjects (73 mmHg, $t = 1.61$, NS). There was also no significant difference in peak UOS SPT pressure nor in any wet swallow parameter between the two groups.

Results in the patients studied with the Gaeltec catheter show marked differences in wet swallow parameters compared with the control values (Table 5.1). Arndorfer catheter measurements of

FIGURE 5.1 - Relationship of AET with Maximum Tonic UOS Pressure (Arndorfer) C = control, G = globus, V = dysphonia, $ = multiple occurrence

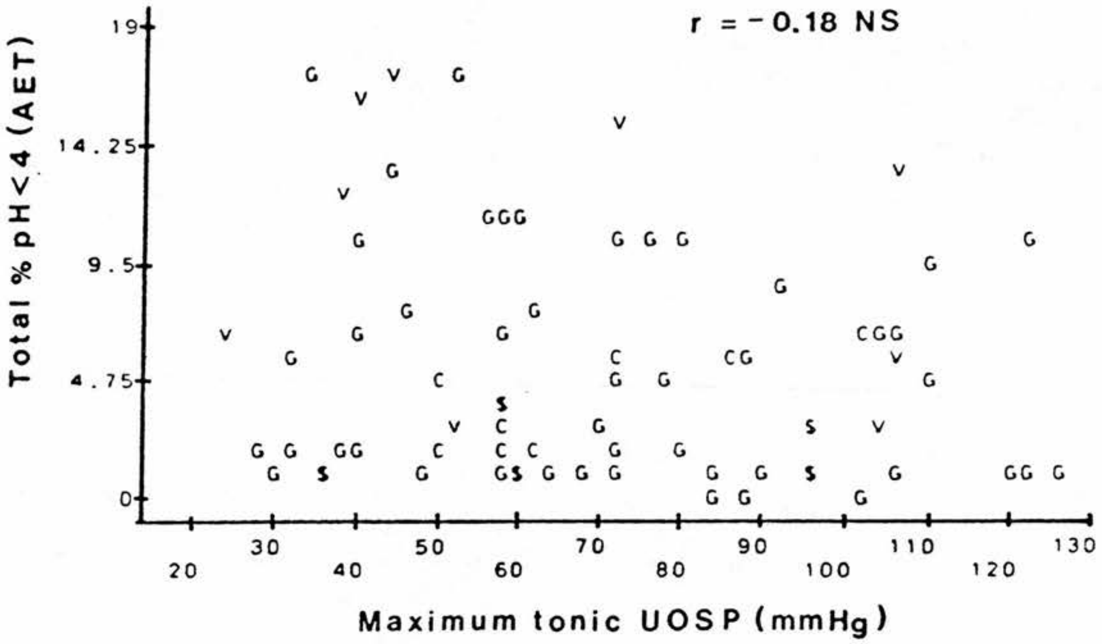
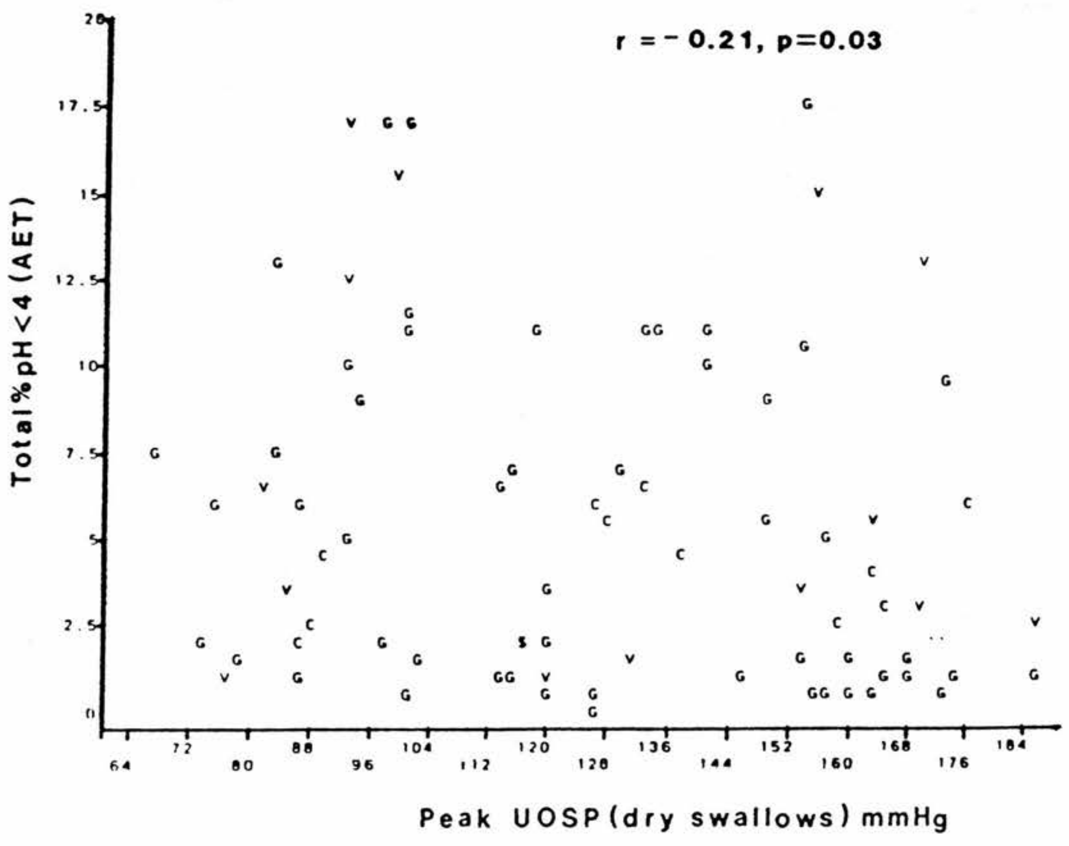


FIGURE 5.2 - Relationship of AET with Peak UOS SPT Pressure (Arndorfer) Symbols as for Figure 5.1



wet swallow after-contraction amplitude were also significantly higher in patients than in controls ($p < 0.05$). Regression analysis revealed, however, no association of AET with wet swallow duration, UOS after-contraction or pharyngeal contraction with either the Arndorfer or the Gaeltec catheter. Full details of manometric parameters in patients with globus sensation are given in Section 6.4.2. There was also no correlation of LOS pressure with maximum tonic UOS pressure ($r = 0.06$ Arndorfer, $r = 0.03$ Gaeltec) or with peak SPT UOS pressure ($r = -0.12$ Arndorfer, $r = -0.01$ Gaeltec). LOS pressure was not significantly associated with any wet swallow parameter in either the Arndorfer or the Gaeltec groups.

5.1.4 <u>Discussion</u>

Early manometric studies of the effect of GOR suggested that reflux induced an elevation in UOS pressure which could, in turn, lead to the formation of a pharyngeal pouch (Hunt et al 1970, Smiley et al 1970). The studies were performed, however, with a recording system which would now be regarded as inadequate and, as the authors themselves noted, the control subjects had unusually low UOS pressures. A later report failed to confirm an association of UOS pressure with 15 hour pH monitoring (Stanciu and Bennett 1974). A retrospective study of the correlation of LOS and UOS pressure also rejected the 'teleologically appealing' theory that reduction in LOS pressure provoked a protective rise in UOS pressure to prevent oesophagopharyngeal reflux (Berte and Winans 1977). Henderson et al (1976) demonstrated incoordination of pharyngeal contraction with UOS relaxation in half of their patients with cervical dysphagia secondary to GOR but their later work showed no association of such incoordination with dysphagia, no increase in UOS tone in patients selected for cricopharyngeal myotomy and a 'puzzling persistence' of dysphagia following hiatal repair (Henderson and Marryatt 1977). Later studies reported no association of hypertensive UOS with GOR (Winship 1983) and no alteration in UOS pressure following documented reflux episodes on pH monitoring (Kahrilas et al 1987b).

The present results are in keeping with the majority of previous reports of the effect of GOR on UOS function. Using two different methods of UOS pressure measurement and prolonged pH monitoring to quantify GOR in 123 subjects, no correlation of AET and tonic or peak UOS pressure on SPT has been demonstrated. Mean tonic UOS pressure was also found to be no greater in 25 patients with both clearly prolonged total oesophageal AET and cervical symptoms than in subjects without demonstrable reflux. There was also no association of LOS and UOS pressures with either the Arndorfer or the Gaeltec catheter. In the larger group studied with the Arndorfer catheter, there was a significant fall in maximum tonic UOS pressure with age and a trend towards a similar reduction in peak SPT UOS pressure. The reduction in UOS pressure with age, attributed to degeneration of striated muscle (Weihrauch et al 1980b) is discussed in Chapter 4. In addition, the detailed analysis of wet swallow parameters has failed to show any association of swallow duration, UOS after-contraction or pharyngeal contraction with GOR as assessed by prolonged pH monitoring. This is an important finding because in these parameters there are differences between controls and patients with cervical symptoms. These abnormalities are described fully in Section 6.4 but it should be noted that the abnormalities of pharyngo-oesophageal motility do not appear to be related to GOR as assessed by prolonged pH monitoring.

In conclusion, oesophageal acid exposure time is not associated with tonic or deglutition pressures in the pharyngo-oesophageal segment. UOS pressure measurements are much more influenced by age and by recording system variables than by the extent of GOR.

5.2 THE EFFECT OF ACUTE OESOPHAGEAL ACID EXPOSURE ON UPPER OESOPHAGEAL SPHINCTER PRESSURE

5.2.1 Methods

A modified Bernstein test was performed with the sleeve catheter linked to the GR800 recorder. A preliminary SPT of the UOS at 0.5 cm intervals was performed with the sleeve sensor orientated posteriorly, where possible, to locate the site of maximum tonic UOS pressure. The sleeve sensor was repositioned with its proximal end at this level in order to obtain a stable baseline tonic pressure recording, not subject to undue fluctuation during spontaneous dry swallows (see Section 4.2). Perfusion in the proximal side-holes was discontinued to reduce the frequency of dry swallows. The oesophagus was perfused at 4 ml/min, 10 cm below the UOS with (a) 0.9% NaCl for five minutes, (b) 0.1N HCl for 15 minutes and (c) 0.1N $NaHCO_3$ for two minutes. Any symptoms experienced by subjects during the test were recorded and where these were severe, the test was discontinued.

5.2.2 Subjects

The acid perfusion test was performed in 15 healthy volunteer control subjects and in 12 patients. In seven of the patients the principal complaints were of globus or cervical dysphagia. The remaining five patients had typical symptoms of GOR.

Data were analysed by paired Student's t-test.

5.2.3 Results

Perfusion of the upper oesophagus with 0.9% NaCl caused no alteration of tonic UOS pressure. There was no significant increase in UOS tone following 15 minutes of 0.1N HCl perfusion. Mean UOS pressure during infusion with 0.9% NaCl was 47 mmHg (SD = 26). During 15 minutes of 0.1N HCl perfusion mean pressure was

48 mmHg (SD = 26). During two minutes 0.1N $NaHCO_3$ perfusion, mean pressure was 50 mmHg (SD = 27). The test was symptomatically positive in three of the patients with suspected GOR, necessitating termination of HCl infusion at 6 to 10 minutes. None of these patients demonstrated a concomitant increase in UOS pressure. The mean increment of UOS pressure during HCl infusion was 1.3 mmHg (SD = 7.7) and during $NaHCO_3$ infusion, the mean increment was 2.4 mmHg (SD = 9.0). During the initial experiments it became apparent that head movement induced large but transient fluctuations in UOS pressure due to catheter rotation. Subjects were instructed subsequently to maintain a stable head posture.

5.2.4 Discussion

While most previous reports of physiological reflux showed little association with UOS function (Section 5.1.4), there has been much greater controversy over the effect of acute experimental acid infusion on UOS pressure. Stanciu and Bennett (1974) found no alteration of UOS pressure following 0.1N HCl acid perfusion of the oesophagus 10 cm below the UOS but infusion was continued for only three minutes and a syringe-pump manometric system was used with only one port in the sphincter. A later Scandinavian study using a low-compliance system (Wallin et al 1978) showed only a short duration increase in UOS tone at one minute during lower oesophageal acid infusion which reverted to normal by five minutes and which may have constituted an arousal response (Satha et al 1985). Gerhardt et al (1978) performed UOS SPTs after acid infusion, controlled for arousal by sham infusion and showed increases in UOS tone after both NaCl and HCl infusion. The response was more marked if large volumes of acid were used (up to 11 ml/min or 50 ml in a few seconds) and if the infusion were close to the UOS. The response was noted to be absent in patients with oesophagopharyngeal reflux (Gerhardt et al 1980a). The response of UOS SPT pressure in dogs was studied by Freiman et al (1981) who found that an infusion rate of greater than

5 ml/min was required to elevate UOS pressure. In contrast to Gerhardt's findings, NaCl infusion produced no alteration of UOS tone. In both normal infants and infants with GOR, a minimal acid stimulus (3 ml in one minute) was noted to produce a 10 cmH_2O increase in UOS pressure, although resting UOS pressure was similar in the two groups (Sondheimer 1983).

The present finding of unaltered UOS pressure before, during and after 0.1N HCl infusion at 4 ml/min, 10 cm below the UOS is, therefore, at variance with most early reports. It is possible that UOS pressure augmentation might have been noted had greater amounts of acid been infused more quickly, but this would have produced volume effects which it was sought to minimise as there is little doubt that oesophageal distension produces a reflex increase in UOS pressure (Satha et al 1985, Andreollo et al 1988). Use of the sleeve sensor in the present study allowed continuous measurement of UOS pressure during infusion, as opposed to pull-through recording after a period of infusion. While the infusion of a large bolus of acid over a few seconds may indeed produce a transient elevation of UOS pressure, the effect of so unphysiological a stimulus is of doubtful clinical relevance (Kahrilas et al 1987b). Furthermore, the normal basal UOS pressure is quite sufficient to protect against oesophago-pharyngeal reflux (except perhaps during deep sleep). In the present study, tonic UOS pressure was, however, recorded just below the zone of maximum sphincter pressure (to prevent swallow-interference with baseline recording). Thus, a change in UOS tone localised to the area just above the sleeve sensor may not have been detected. If oesophageal acid infusion were to influence a vagal reflex arc, then the efferent limb of such a reflex might act only on the cricopharyngeal segment of the high pressure zone. Further studies are, therefore, planned to establish whether the results of the present study can be reproduced with the sleeve sensor sited more proximally.

Thompson et al (1988) recorded UOS pressure for a few minutes following oesophageal balloon distension or infusion with 0.1N HCl or saline at varying rates and increasing distance from the sphincter. Very similar UOS pressure rises were recorded following all three manoeuvres and it was concluded that the principal stimulus was oesophageal distension rather than pH change. There have been two other preliminary reports of the use of the sleeve sensor to monitor the response to acid infusion. Anvari et al (1988) noted no increase in UOS pressure during intraoesophageal infusion of saline or 0.1N HCl at 7 ml/min. An increase in spontaneous swallow frequency was, however, observed and the resultant increase in oesophageal clearance was thought to contribute to upper airway protection. Vakil et al (1988) used a sleeve sensor to monitor UOS pressure during 25 minutes of mid-oesophageal infusion with 0.1N HCl at 2 ml/min. The results confirm the findings of the present study as there was no significant alteration in UOS tone either in controls or in patients with oesophagitis. Results also confirm the present findings (Section 5.1.3) of normal UOS tonic pressure in patients with GOR.

In conclusion, the reported effects of intraoesophageal acid perfusion on the UOS vary according to the volume of acid used and the method of UOS pressure measurement. Transient UOS pressure augmentation must be differentiated from arousal responses and the continuous recording of UOS pressure with a sleeve sensor is probably preferable to the performance of post-infusion pull-throughs, although movement artifacts must be eliminated by careful observation and instruction of subjects. Where the sleeve sensor has been used, as in the present report, there is no evidence of significant UOS pressure alteration in response to oesophageal acid perfusion.

5.3 THE AETIOLOGY OF POSTERIOR LARYNGITIS

Twenty years ago, while some workers were describing an augmentation of UOS pressure in response to GOR which might lead to pharyngeal pouch formation, others were proposing that GOR, in association with an incompetent UOS and oesophagopharyngeal reflux, might produce laryngeal pathology (Cherry and Margulies 1968, Delahunty 1972). The principal aim of the present study was to compare two objective measurements of GOR (prolonged ambulatory pH monitoring and oesophageal biopsy) with the findings on posterior laryngeal biopsy. Having identified patients with interarytenoid histological abnormality, analysis of UOS pressures was performed to see whether laryngeal disease was related to UOS incompetence.

5.3.1 Methods

Detailed laryngeal history and examination were performed in the dysphonia clinic, followed by videolaryngoscopic and stroboscopic inspection of the larynx. These examinations were performed by Dr Aileen White. Direct enquiry about gastrointestinal symptoms was made and heartburn was scored as 0 - no heartburn; 1 - less than once per month; 2 - less than once per week or 3 - more than once per week.

Prolonged ambulatory pH monitoring was performed all but one patient - an elderly male who declined this investigation. The method used has been described in Section 5.1.1. During this study, not only the percentage total time of pH less than 4 but also the erect and recumbent AETs, the total number of reflux episodes, the longest episode and the total number of episodes greater than five minutes were recorded. In 64 patients, an Arndorfer catheter was used to record maximum tonic UOS pressure as described in Section 5.1.1

Patients underwent a barium meal examination followed by direct laryngoscopy and rigid oesophagoscopy under general anaesthesia. Biopsies were taken of any structural abnormality and from the interarytenoid area of the larynx and the distal oesophagus, at least 2 cm above the squamo-columnar junction. All specimens were examined by Dr Juan Piris who was not informed of the results of the other investigations.

For reasons discussed in Section 5.3.4, the upper limit of normal total AET was taken as 10% and this parameter was used to distinguish normal from abnormal GOR. Any patient with a total AET of 10% or greater and/or whose distal oesophageal biopsy showed evidence of acute or chronic inflammatory infiltrate was classed as a 'reflux patient'.

5.3.2 Subjects and Data Analysis

During the 10 month period of the study, approximately 200 patients were seen in the dysphonia clinic. For ethical reasons it was clearly unacceptable to study all attenders by the methods outlined above. Ninety seven patients were, therefore, selected for study. Ten patients had a principal complaint of globus sensation without heartburn or marked vocal symptoms. These were included as there were no controls (for ethical reasons) for the radiological or endoscopic parts of the study and it was thought possible that the remaining 87 patients might all demonstrate laryngeal abnormalities and/or GOR. These 87 patients were all selected on the basis of the classically accepted clinical features of so-called 'acid laryngitis' - grade 2 to 3 heartburn in association with vocal symptoms and/or globus sensation; burning pharyngeal discomfort; unexplained nocturnal coughing or choking; or evidence of posterior laryngeal inflammation or pachydermia at laryngoscopy. The age range of the patients was 22 to 86 years ($\bar{X}$ = 50 years).

pH monitoring results were compared with those of 54 control subjects. One control group comprised 34 asymptomatic volunteers, 27 males and 7 females, aged 19 to 67 years (X = 34 years), who were hospital medical and paramedical staff and healthy members of the Royal Naval staff. I am most grateful to these subjects for their participation in the study. The remaining 20 control subjects, seven males and 13 females, aged 31 to 69 years, had been referred to Dr R C Heading for the investigation of non-cardiac chest pain. All of the chest pain control group had normal barium meal, manometry, endoscopy and distal oesophageal biopsy; 12 admitted to occasional heartburn on direct inquiry.

Results were analysed using unpaired Student's t-test, X^2 test with Yates' correction and the Wilcoxon rank sum test.

5.3.3 Results

On the basis of the pH monitoring and oesophageal and laryngeal biopsy results, patients were classified into four groups - no laryngitis with reflux; laryngitis with reflux; laryngitis, no reflux; and no laryngitis, no reflux. The clinical features of these groups are summarised in Table 5.2. Mean age was similar in all four groups. Grade 2 or 3 heartburn was much more common in the two reflux groups (82%) than in the two non-reflux groups (32%) ($X^2 = 13.6$, $p < 0.001$). As expected, the 10 patients with isolated globus sensation are among the 42 with neither laryngitis nor reflux. Burning pharyngeal discomfort was present in only four laryngitis patients, three of whom had reflux. Almost one third of patients were cigarette smokers, whose numbers were significantly greater in laryngitis patients without reflux.

pH monitoring results are illustrated in Figures 5.3 to 5.6. Patients in the reflux groups with total AET less than 10% were classified as refluxers on the basis of histological oesophageal inflammatory infiltrate (Figure 5.3). Total and upright AETs were log-transformed prior to analysis by Student's t-test. The

TABLE 5.2 **Clinical Features of Patients with Suspected Acid Laryngitis**

GROUP	n	M	F	AGE (years) Mean (SD)	HEARTBURN GRADE 2/3	HOARSE	GLOBUS	SMOKERS
Reflux, no laryngitis	14	4	10	49.3 (14.3)	10	7	11	6
Reflux, laryngitis	17	9	8	54.8 (12.9)	13	13	9	5
Laryngitis, no reflux	24	3	21	47.0 (14.3)	7	13	20	13*
No laryngitis, no reflux	42	14	28	49.6 (11.3)	14	20	39	9
TOTAL	97	30	67	50.3 (13.3)	44	53	79	33

* $X^2 = 3.84$, $p = 0.05$ compared with patients without laryngitis

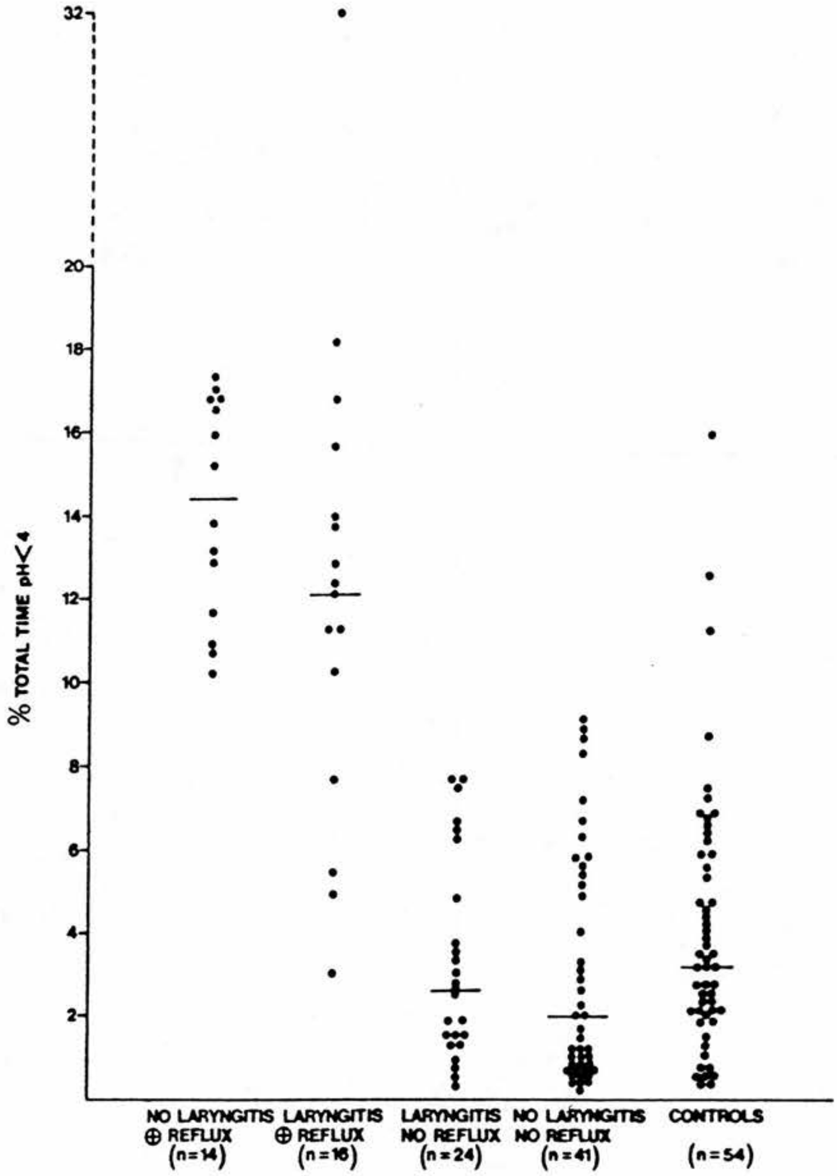


FIGURE 5.3 - Percentage Total Time of Intra-oesophageal pH less than 4 in Patients and Controls
(Medians are indicated)

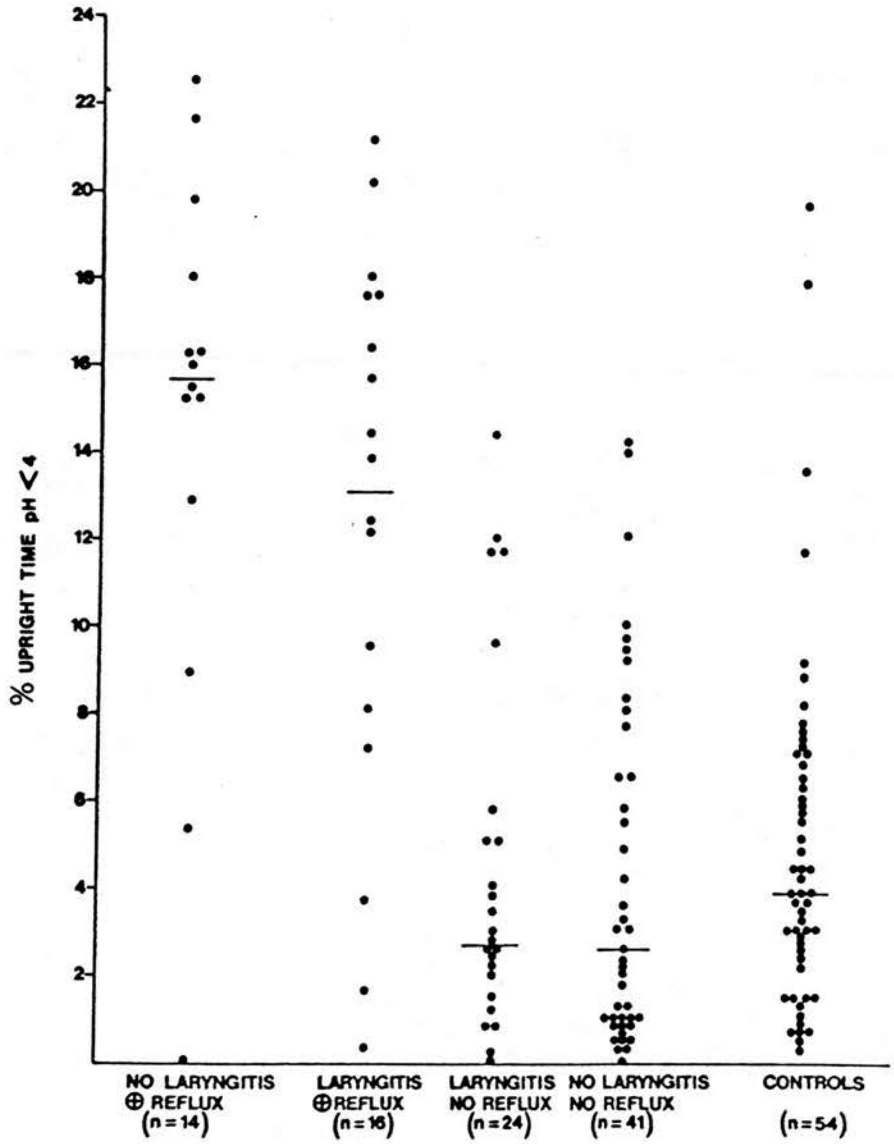


FIGURE 5.4 - Percentage Upright Time of Intra-oesophageal pH less than 4 in Patients and Controls

(Medians are indicated)

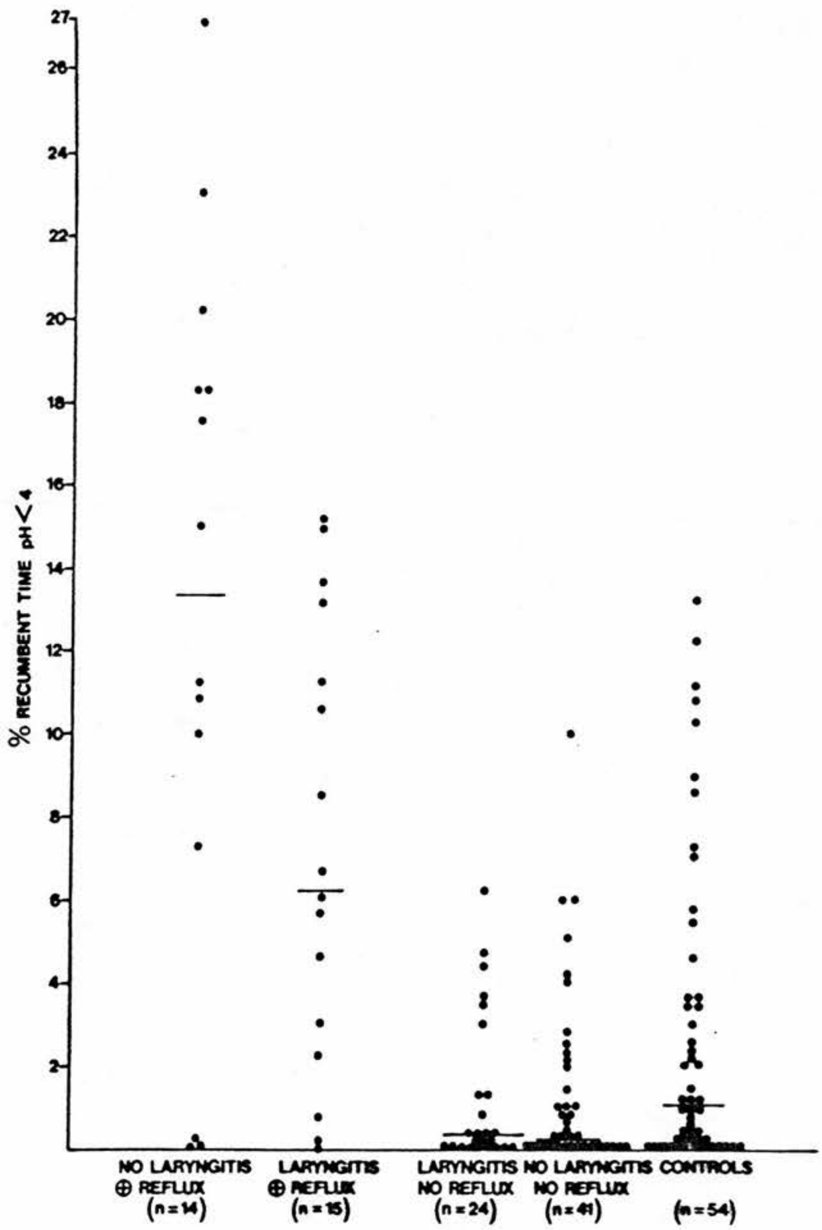


FIGURE 5.5 - Percentage Recumbent time of Intra-oesophageal pH less than 4 in Patients and Controls

(Medians are indicated; one subject with laryngitis and reflux not shown)

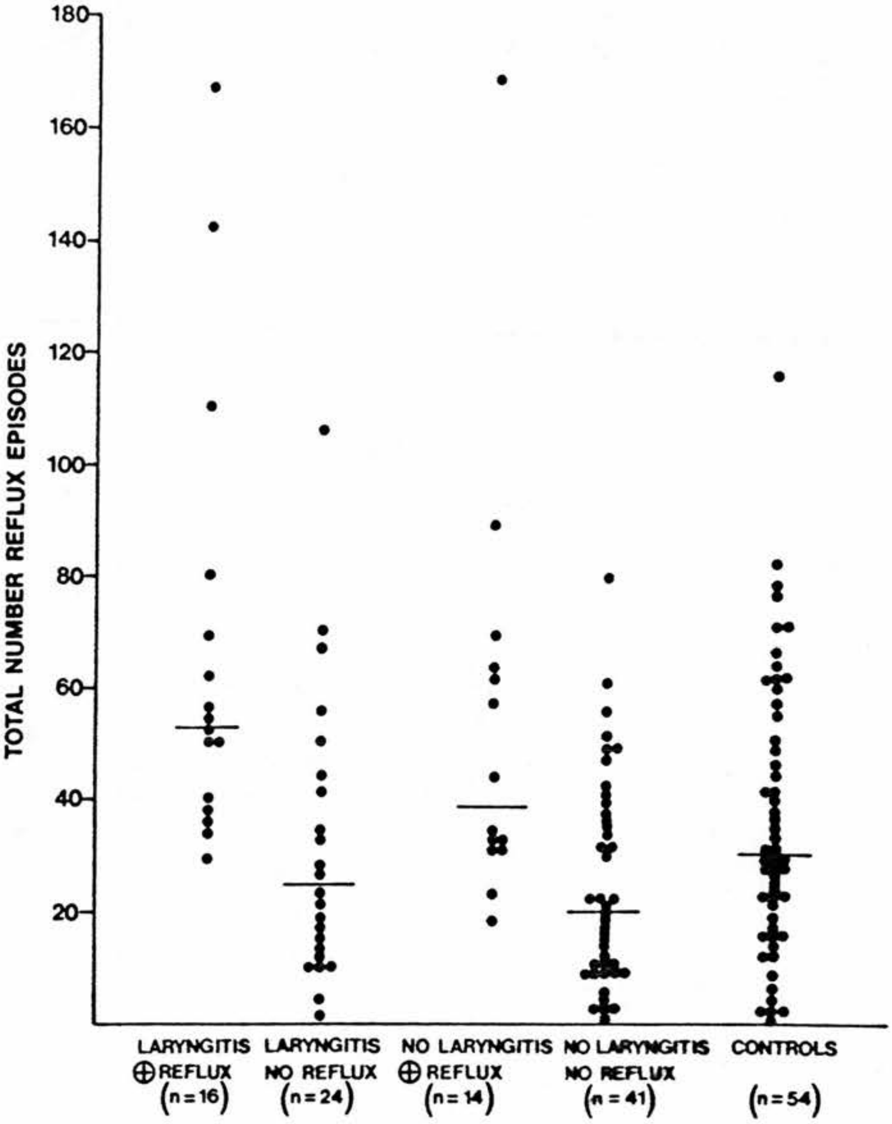


FIGURE 5.6 - Number of Episodes of Intra-oesophageal pH less than 4 in Patients and Controls (Medians are indicated)

large number of individuals with no recumbent reflux (Figure 5.5) precludes log-normalisation and these data were, therefore, analysed by the Wilcoxon rank sum test. The reflux groups both demonstrated significantly greater AET for the total period ($p < 0.001$) and for the upright and recumbent periods ($p < 0.01$) when compared with control subjects (Table 5.3). The total number of reflux episodes was not a useful discriminant (Figure 5.6), whereas the number of episodes greater than five minutes' duration confirmed the prolonged acid exposure in the reflux patients. Twenty two of the reflux patients had more than six episodes of greater than five minutes' duration, compared with only three of the non-reflux patients and three of the controls ($X^2 = 38.9$, $p < 0.001$). There was no significant difference between reflux patients with and without laryngitis in total, upright or recumbent AETs, nor in the number of episodes greater than five minutes. Total AET was no greater in smokers than in non-smokers.

Mean maximum tonic UOS SPT pressure was 76 mmHg (SD = 30) in 26 patients with no laryngitis and no GOR. UOS pressure was not significantly different in the 11 patients with GOR only (70 ± 26 mmHg) nor in the 16 with laryngitis only (68 ± 30 mmHg). In the 11 patients with both GOR and laryngitis, however, there was a trend to lower maximum tonic UOS pressure (50 ± 23 mmHg, $t = 1.91$, $0.1 > p > 0.05$).

The pathological findings in the 41 patients with posterior laryngeal biopsy abnormality are listed in Table 5.4. The commonest finding was of a chronic inflammatory infiltrate, usually of mixed cell type but on occasion with predominant lymphocytes or mast cells. Parakeratosis was often seen in conjunction with other abnormalities. No pathological change was observed to be characteristic of reflux and, overall, the changes were mild.

TABLE 5.3 - Geometric Mean and Median AET

GROUP	GEOMETRIC MEAN TOTAL	GEOMETRIC MEAN UPRIGHT	MEDIAN RECUMBENT
No laryngitis with reflux	13.98**	10.35*	13.2+
Laryngitis with reflux	10.76**	7.20*	7.6+
Laryngitis, no reflux	2.21	2.48	0.3
No laryngitis, no reflux	1.87	2.42	0.2
Controls	2.97	3.57	1.0

* $p < 0.01$, ** $p < 0.001$ Student's t

\+ $p < 0.01$ Wilcoxon rank sum

TABLE 5.4 - Laryngeal Pathology (n = 41)

	No	REFLUX (n = 17)	SMOKERS (n = 18)
Interarytenoid			
Chronic inflammation	27	10	13
Parakeratosis	15	7	7
Submucosal scarring	2	2	-
Oedema	2	1	-
Vocal Cord			
Nodule	2	1	2
Inflammation	2	2	-
Post Cricoid			
Web	2	-	1

5.3.4 **Discussion**

This is the first report of the use of pH monitoring to investigate substantial numbers of patients with suspected laryngitis. Forty one patients with posterior laryngeal biopsy abnormalities have been identified, of whom 17 (41%) had objective evidence of GOR (Table 5.4). Thus the incidence of reflux-associated laryngitis in the 87 patients suspected on clinical grounds to have this condition was less than 20%. There are two areas of difficulty when comparing our results with those of previous investigators. The first is patient selection. Wiener et al (1986a) claimed that 80% of 14 patients with chronic hoarseness had at least one abnormal pH parameter, but the group was extremely heterogeneous in terms of laryngeal disease and selection criteria were unclear (see also Section 3.2). The present series of patients was selected from over 200 dysphonia clinic attenders during the study period in whom the 17 with GOR-associated laryngitis represents an incidence of only 8.5% in dysphonic patients overall. A decreasing incidence of reflux in ENT patients referred for gastrointestinal investigation has also been observed by Wiener's group, and has been attributed to alterations in patient selection (D O Castell, personal communication 1988).

The second problem arises from the use of pH monitoring to define abnormal GOR. The technique is clearly superior to other methods in the diagnosis of reflux (see Section 2.3) and is undoubtedly preferable to the use of clinical features such as heartburn. The overall incidence of heartburn more than once monthly in the present series was 30%, ie similar to the general age-matched population, although significantly more common in patients with documented GOR. Normal pH monitoring data do not conform to a normal distribution (Figure 5.3). Because of the positive skew of AETs in asymptomatic subjects, it is not possible to define a normal range based on arithmetic mean and standard deviation. Comparison of normal pH data with results of subjects with GOR disease confirmed by other tests led Schindlbeck et al (1987b) to propose that a combination of 10% upright AET with 6% recumbent AET be used to define the upper limit of normality. Previous reports are in disagreement, however, about the relative importance of diurnal and nocturnal reflux in the aetiology of laryngitis and it was, therefore, decided to use total AET as the discriminant factor in the present study. The 10% upper limit of total AET corresponds to the geometric mean plus 1.6 SD of log-transformed data, likely to include 87% of the normal population. This figure, although higher than the early reported upper normal limits obtained on subjects screened for oesophageal disease before study, and studied under more restricted conditions, is in keeping with more recent reports (Shaker et al 1988b, Smout et al 1988), and is more likely to reflect the limits of physiological reflux under restricted circumstances. To minimise any possible false negative pH monitoring results, however, pH data were not analysed in isolation but in conjunction with oesophageal biopsy findings. These were abnormal in patients with total AET of less than 10% (Figure 5.3). Use of the two methods in combination as advocated by Vitale et al (1984) makes it unlikely that any significant degrees of GOR were overlooked in the patients studied.

The response of the distal oesophageal epithelium to physiological and pathological degrees of GOR has been well-documented (Weinstein et al 1975, Johnson et al 1978). The histological response of upper respiratory tract epithelium to acid has been examined only in experimental animal studies (Delahunty and Cherry 1968, Wynne et al 1981, Little et al 1985). These bear little relationship to in vivo laryngeal acid exposure. A recent study of human foetal laryngeal epithelium has indicated that squamous epithelium is commonly found in extra-glottic sites even in utero, thus questioning the commonly held theory of secondary squamous metaplasia (Stafford and Davies 1988). The interarytenoid epithelium in all subjects in the present study was also of stratified squamous and not of respiratory type. Although none of the subjects biopsied was entirely asymptomatic, 10 had isolated globus sensation only, and in view of the large numbers of individuals biopsied (97) it seems reasonable to conclude that the normal adult interarytenoid epithelium is of the squamous type. Although Chodosh (1977) attributed post-cricoid webs to GOR, neither patient with a web in the present series had evidence of reflux.

Eighteen of the 41 patients were cigarette smokers (Table 5.4). Cigarette smoking has been shown not to inflence AET (Schindlbeck et al 1987a), a finding confirmed in the present study and the incidence of smoking was higher in those patients whose laryngeal abnormalities were not associated with GOR (Table 5.2). The relatively small number of smokers in the group with both reflux and laryngitis confirms previous reports (Ohman et al 1983, Katz et al 1988, J E Richter, personal communication 1987) and tends to support reflux as a genuine aetiological factor in at least some patients. Similarly, there is some indirect evidence that reflux may be an aetiological factor for laryngeal carcinoma in the small number of non-smoking patients with this disease (Morrison 1988, Ward and Hanson 1988). On the other hand, 11 patients with posterior laryngeal biopsy abnormalities had no GOR nor were they smokers. The aetiology of laryngitis in this group remains unknown, as does the aetiology of dysphonia in the 20 patients with neither reflux nor laryngitis who complained of hoarseness. Vocal abuse, as originally suggested by Chevalier Jackson (1928) to be the aetiology of contact ulcer of the larynx, may be important. None of the patients attending the dysphonia clinic during the 10 month study period showed evidence of contact ulceration and the disease may show distinct demographic patterns as most series have been described in North American populations. Even those who claim an associated high incidence of oesophageal dysfunction emphasise the importance of underlying stress and of voice therapy in contact ulceration (Ohman et al 1983).

Of the 31 patients with GOR, 20 complained of hoarseness (Table 5.2) but three of these had no pathological abnormality in the larynx. While micro-aspiration of acid might produce symptoms in the absence of histological abnormality, it is more likely that these patients suffer from the chance coincidence of two phenomena (GOR and hoarseness) which are common in middle age. By the same token, it is also possible that in some of the other reflux laryngitis patients, GOR is an incidental rather than a causal association. None of the pathological changes described was characteristic of patients with GOR. Also, no particular abnormality of pH monitoring characterised GOR patients who also had laryngitis, confirming the findings of Wiener et al (1986a). It has been proposed that there is a higher incidence of upright reflux in small numbers of patients with heterogeneous laryngeal pathology (Katz et al 1988) but this was not confirmed in the present much larger population with a large control sample (Table 5.3). Upright reflux has, however, been shown to be more common than supine reflux both in patients with GOR and in controls (Shaker et al 1988b). Similarly, although nocturnal coughing or choking has been claimed to indicate recumbent GOR in patients with laryngeal disease, recumbent reflux was rare in the present group (Figure 5.5) and no more common in those with laryngitis (Table 5.3). Wiener et al (1986a) and Katz et al (1988) also reported a high incidence of normal endoscopic findings in patients with reflux-associated chronic hoarseness but only three of 17 reflux laryngitis patients in the present study had normal oesophageal biopsy findings. This may reflect either differences in patient selection or criteria for abnormality on pH monitoring.

It was not possible to perform dual pharyngo-oesophageal pH monitoring in the present study. Wiener et al (1986b) found pharyngeal reflux to be much less common than pharyngeal pseudoreflux (See also Section 3.2). Katz et al (1988) demonstrated pharyngeal reflux episodes in three patients with normal oesophageal pH monitoring, but no control values for hypopharyngeal reflux were reported. Pearlman et al (1988) have suggested that patients with reflux and cervical symptoms such as globus or hoarseness respond poorly to medical therapy because of an associated low cricopharyngeal tone. In the reflux-associated laryngitis group in the present study, the finding of a trend to lower Arndorfer catheter measurements of UOS tonic pressure compared with patients with only GOR or laryngitis or neither of these may provide indirect evidence to support the presence of oesophago-pharyngeal reflux (Gerhardt et al 1980a) but the numbers in each group are small (other subjects having been studied by different manometric methods). Also, basal UOS tone may not be the only important determinant of oesophagopharyngeal reflux.

Delahunty (1972) proposed that retrograde peristalsis secondary to reflux produced a sub-cricopharyngeal tension bolus and that swallow-induced UOS relaxation allowed the bolus to regurgitate into the hypopharynx. In the lower oesophagus, reflux of gastric contents is associated with transient inappropriate LOS relaxations (Dent et al 1980, Mittal and McCallum 1988) but there is no evidence that swallow-induced relaxation of the UOS causes oesophagopharyngeal reflux. If anything, the oesophageal peristalsis and salivary neutralisation following a swallow (Helm et al 1982) are more likely to improve oesophageal acid clearance. Kahrilas et al (1986) have, however, demonstrated transient UOS relaxations following belching or in response to upper oesophageal distension by air. Such relaxations are of longer duration than swallow-induced relaxations of the UOS, and are not accompanied by primary peristalsis. Furthermore, the relaxation during belching occurs when there is a gastro-oesophageal common cavity pressure rise, whereas swallow relaxations are usually accompanied by a negative cervical oesophageal pressure, ie by a pharyngo-oesophageal pressure gradient. In contrast, fluid boluses do not produce a UOS relaxation (Kahrilas et al 1986) and the importance of LOS relaxation, belching and transient UOS relaxation in oesophagopharyngeal reflux and acid laryngitis remains speculative. Similarly, the importance of respiratory effects on sphincter tone remains unclear. On inspiration the combination of increased intra-abdominal pressure with reduced intrathoracic pressure tends to increase GOR (Mittal and McCallum 1988) while the inspiratory increase in UOS tone and the increased pharyngo-oesophageal pressure gradient are likely to prevent oesophagopharyngeal reflux.

In conclusion, evidence of concurrent GOR and posterior laryngeal pathology was found in 17 of 97 patients studied. Fourteen patients had reflux without laryngitis and 24 had laryngitis without demonstrable GOR disease. Cigarette smoking appears to be a further aetiological factor in posterior laryngitis, whose cause was unexplained in 11 patients. Although the incidence of reflux-associated posterior laryngitis must depend to some extent on patient selection, it is concluded that these findings reflect the true incidence more accurately than studies based on clinical impressions or on uncontrolled trials of medical therapy, many of which involve cessation of smoking and in none of which was the placebo component assessed. The importance of UOS incompetence in the aetiology of acid laryngitis remains to be established.

6. GLOBUS PHARYNGIS

6.1 OESOPHAGOSCOPY IN ENT PRACTICE

The majority of ENT departments in the United Kingdom perform endoscopic examination under general anaesthesia using rigid oesophagoscopes, as the examination is frequently performed in association with direct laryngoscopy. Rigid oesophagoscopy is a costly and potentially hazardous procedure which requires hospitalisation and is associated with a perforation rate of 0.11 to 1.9% (Swamy and Rayl 1978, Wesdorp et al 1984, Borgeskov et al 1984). The examination has a high incidence of negative findings in ENT practice. The aim of the present retrospective study was to assess the indications for and complications of the procedure, and to compare the diagnostic yield with that of conventional barium radiology in a district general hospital. Particular attention was given to the incidence of negative findings and to the role of globus pharyngis in ENT endoscopic practice.

6.1.1 <u>Methods</u>

From 1975 to 1985, 204 patients, 133 females and 71 males, underwent elective rigid oesophagoscopy at Bangour General Hospital, West Lothian. In 133 patients direct laryngoscopy was performed at the time of oesophagoscopy. Case records for all patients were reviewed and clinical features compared with abnormalities on barium radiology and endoscopy. The management of patients with normal oesophagoscopy was reviewed.

6.1.2 <u>Results</u>

No abnormal findings were present on oesophagoscopy in 145 patients (71%). Of 133 patients undergoing direct laryngoscopy, 105 (79%) had no demonstrable abnormality. Both examinations were normal in 57% of patients of both sexes. Globus sensation was the most common symptom, being present in 120 patients, 76 females and 44 males, of whom 93 (77.5%) had normal oesophagoscopy. In 60 patients globus was the sole symptom and 83% of these had a normal oesophagoscopy. The incidence of normal findings on both laryngoscopy and oesophagoscopy is shown in Table 6.1. Normal findings were much less common in patients with dysphagia or hoarseness. In 12 patients with pharyngeal or oesophageal carcinoma the major symptoms were dysphagia (ten), weight loss (seven) and hoarseness (five), although two patients also had globus sensation (Table 6.2). The most common oesophagoscopic findings in globus were oesophagitis in 14 patients and cricopharyngeal spasm in eight patients.

Barium examination and oesophagoscopy were both normal in 85 patients (42%). Of the 57 patients (28%) in whom no barium study was performed, 49 had a normal oesophagoscopy and the remaining eight had GOR (three patients), cricopharyngeal spasm (two patients), prominent osteophytes, a benign stricture and a clinically obvious hypopharyngeal carcinoma. Oesophagoscopic and radiological findings in the remaining 62 patients (30%) are summarised in Table 6.3. Barium examination detected three small pharyngeal diverticula and five hiatus herniae not noted at endoscopy, while endoscopy had a higher yield of carcinoma and of cricopharyngeal spasm. Fewer than 40% of diagnoses were made at both examinations.

Two of the six complications of oesophagoscopy (2.9%) followed normal examinations - one aspiration pneumonia and one lower oesophageal perforation. Perforation also followed dilation of a benign stricture. The other complications were a tension pneumothorax, surgical emphysema following a Dohlman's procedure and fatal aspiration pneumonia in an elderly patient following biopsy of a posterior pharyngeal wall carcinoma.

Only 16 of 117 patients (14%) in whom both laryngoscopy and oesophagoscopy were normal were offered treatment. Antacids were prescribed to seven patients, only one of whom had evidence of

TABLE 6.1 - Major Presenting Symptoms of ENT Patients Undergoing Endoscopy

SYMPTOM	NO	LARYNGOSCOPY AND OESOPHAGOSCOPY NORMAL	(%)
Globus	120	82	(68)
Dysphagia	58	22	(37)
Hoarseness	34	12	(35)
Pain	19	15	(79)
Weight loss	18	4	(22)
Heartburn	11	5	(45)

TABLE 6.2 - Endoscopic Findings Associated with Globus

Oesophagoscopy	-	GOR/Oesophagitis	14 (4)
		Cricopharyngeal spasm	8 (3)
		Post-cricoid carcinoma	2
		Stricture	2 (1)
		Osteophytes	2 (2)
		Web	1
Laryngoscopy	-	Laryngitis	5 (1)
		Lingual tonsillitis	4 (2)
		Vallecular cyst	1 (1)
		Tonsil papilloma	1
TOTAL			40*

* Two patients with reflux had a second diagnosis

Numbers in brackets refer to patients with globus alone

TABLE 6.3 - Comparison of the Diagnostic Yield of Oesophagoscopy and Barium Meal in 62 Patients

DIAGNOSIS	NO	OESOPHAGOSCOPY	BARIUM	BOTH
GOR/Oesophagitis	21	9	9	3
Carcinoma (pharynx or oesophagus)	11	4	0	7
Cricopharyngeal spasm	10	4	0	6
Stricture	9	1	0	8
Pouch	6	0	3	3
Hiatus hernia	5	0	5	0
Web	4	1	1	2
Osteophytes	2	2	0	0
External complications	2	1	1	0
Achalasia	1	0	1	0
Gastric ulcer	1	0	1	0
Duodenal scarring	1	0	1	0
TOTAL DIAGNOSES	73*	22	22	29

* 11 patients had GOR or hiatus hernia plus a second diagnosis

GOR disease and five were given mucolytics, diazepam or advice on avoidance of inhaled allergens. Four patients were treated surgically, by tonsillectomy, molar extraction and excision of a lymphomatous node.

6.1.3 Discussion

The 70% diagnostic accuracy of barium radiology in the oesophagus is similar to the 68% accuracy reported by Martin et al (1980). The 28% of patients who did not undergo barium examination would now routinely have this investigation performed prior to oesophagoscopy. Radiology can reveal an unexpected stricture or distortion of anatomy (Mullard 1981) and can prevent accidental perforation of an unsuspected pharyngeal pouch - eight such perforations have been reported in recent literature (Schulze et al 1982, Borgeskov et al 1984, Wesdorp et al 1984). Also, in patients where both radiology and endoscopy were performed, 30% of diagnoses were made by radiology only. Conversely, three cases of hypopharyngeal carcinoma were overlooked on barium examination. Mucosal detail of the hypopharynx can be improved by the use of double-contrast techniques (Gedgaudas-McLees and McClees 1984) but the rapid passage of barium in the pharyngo-oesophageal segment makes direct inspection of the area mandatory where carcinoma is suspected. In the present series, a carcinoma of the lower oesophagus showed only as a degree of achalasia on barium meal. Such 'secondary achalasia' is well-recognised (Swamy and Rayl 1978, Bennett 1984). In another patient, failure to biopsy a stricture at initial endoscopy delayed the diagnosis of carcinoma of the lower oesophagus by six months. A similar case is reported by Malcomson (1968).

There was one oesophageal perforation in the 145 patients with normal oesophagoscopic findings (0.68%). Two of the other complications occurred during therapeutic rather than diagnostic endoscopy. The perforation rate of fibreoptic endoscopy is 0.01 to 0.18% (Silvis et al 1976, Swamy and Rayl 1978, Dawson and

Cockel 1981, Anonymous 1984), but 0.25 to 0.9% where therapeutic endoscopy is performed. The complication rate of fibreoptic endoscopy is also greater where oesophageal rather than gastroduodenal pathology is being sought (Silvis et al 1976) and in the presence of cricopharyneal spasm (Swamy and Rayl 1978). The 2.9% complication rate in the present series of rigid oesophagoscopies is attributable, therefore, not only to the procedure itself but also to the nature of the underlying pathology and to the therapeutic manoeuvres performed. It has also been shown that fibreoptic oesophagoscopic biopsies are inferior to those obtained at rigid endoscopy in the diagnosis of adenocarcinoma of the oesophagus (Lusink et al 1983). The correlation between the endoscopic diagnosis of oesophagitis and the histological appearance has also been shown to be significantly better with the rigid oesophagoscope and this has been attributed to its superior optical qualities and the greater selectivity in taking large biopsies (Monnier and Savary 1984). On the other hand, during rigid endoscopy, abnormalities such as cricopharyngeal spasm or free reflux of gastric contents may be more a reflection of the general anaesthetic administered than of true pathophysiology. Batch (1985) has advocated that fibreoptic endoscopy be adopted in ENT practice. In standard fibreoptic endoscopy, pharyngeal intubation is, of course, performed blindly, but Batch claims that, with experience, a paediatric instrument can be used to examine the pharynx. Despite this claim, however, patients with suspected post-cricoid malignancy were excluded from his study and Olsen (1982) continues to support the use of the rigid instrument.

The results of the present study show that globus sensation is the most common sensation in ENT patients undergoing oesophagoscopy and is associated with a wide range of positive endoscopic findings in one third of patients (Table 6.2). The aetiological significance of these abnormalities remains unclear. Although globus may be present in pharyngeal carcinoma, the associated features (hoarseness, dysphagia, weight loss) in the two such patients in the present series made a diagnosis of globus pharyngis clinically untenable. The female preponderance of post-cricoid carcinoma and the possibility of missing an early pharyngeal neoplasm in patients with globus mean that endoscopy plays an important role in the exclusion of carcinoma in globus patients, despite the high incidence of normal findings. The small number of patients with normal endoscopic findings who were offered treatment reflects a management strategy based on exclusion of carcinoma and subsequent patient reassurance. The need for endoscopy must continue to be considered carefully in globus patients but the exclusion of carcinoma should not be the primary aim of management. A greater understanding of the causes of globus pharyngis would result in a more positive approach to patient management, based on symptom-relief.

6.2 CLINICAL FEATURES OF GLOBUS PHARYNGIS

Following the retrospective study described above, the author established a clinic for the investigation of globus patients in 1985. At the outset, the principal question addressed was whether or not globus is associated with pathological degrees of GOR (Section 6.3). Standard haematological and radiological investigations were also performed to examine some of the other aetiological theories of globus discussed in Section 3.1. The low diagnostic yield of these investigations led to their discontinuation during the latter part of the study during which detailed manometric and psychological investigations were performed: results of these are discussed in Sections 6.4 and 6.5.

6.2.1 Methods

From 1985 to 1987, 210 patients attended the globus clinic, Royal Infirmary, Edinburgh. All patients had a principal complaint of a feeling of something in the throat and had been referred either by their general practitioner or by another member of the ENT department. A detailed structured history of the nature of the globus sensation, associated symptoms and past disease was taken and a full ENT examination performed on all patients. Three patients with major structural abnormalities on examination, two goitres and one supraglottic cyst, were excluded from the study. Of the first 110 attenders, 98 underwent routine full blood count, biochemical screen and estimation of serum folate, vitamin B_{12} and thyroxine. X-rays of sinuses and cervical spine were also performed in these patients. The remaining 12 patients either defaulted from the clinic or experienced resolution of their symptoms prior to clinic attendance.

6.2.2 Results

The principal results are listed in Table 6.4 and Table 6.5. The 207 patients comprised 158 females and 49 males, mean age 48 years (SD = 13). The age distribution in females and males is shown in Figure 6.1. The sex incidence is equal in the third decade with a female preponderance thereafter. Principal clinical features are listed in Table 6.4. Symptom duration ranged from a few weeks to 23 years: four patients had previously undergone multiple negative endoscopic examinations. Lateral and high cervical locations were rare: the commonest site was in the midline at the level of the cricoid. A major life event - eg redundancy, retirement, bereavement, emigration, termination of pregnancy or divorce - could be identified by 25% of patients on direct enquiry.

The responses to direct enquiry about a variety of associated symptoms are listed in Table 6.5. Weight loss was uncommon (10%) and indeed twice as many patients reported problems with weight gain in response to this question. Postnasal drip and hoarseness were both reported in over 40% but some patients clearly admitted to catarrh only because they believed that it must be the cause of the perceived pharyngeal sensation. Few patients appeared to be objectively dysphonic and most experienced slight tiring of the voice. The majority of patients experienced heartburn which was present more than once per month in 35%. The 36 patients with perceived abnormality of bowel function mostly had mild degrees of chronic constipation, but four had been formally diagnosed as having irritable bowel syndrome and eight had mild looseness of bowel motions. Very few of the many patients with previous minor joint problems or sinusitis had sought medical advice for these complaints. Any previous formal psychiatric counselling (11%) had usually been of short duration.

Minor structural abnormalites of the nose or pharynx were observed in 11 patients who subsequently underwent submucous resection of the nasal septum (three patients) or cryosurgery to prominent lingual tonsils (seven patients). One young woman complained of an excessively long uvula, which she could draw forwards into the oral cavity and had developed the habit of

TABLE 6.4 - Characteristics of the Globus Symptom

	FEMALE	MALE	TOTAL (%)	
n	158	49	207	
Mean age (y)	49	46	48	
Smokers	53	17	70	(34)
Choking	74	12	86	(41)
Fear cancer	75	24	99	(47)
Duration < 3 months	19	10	29	(14)
3 - 6 months	58	17	75	(36)
6 - 12 months	35	9	44	(21)
> 12 months	46	13	59	(29)
Site - Medial	121	40	161	(78)
- Lateral	37	9	46	(22)
Level - Thyrohyoid	29	12	41	(20)
- Cricothyroid	72	24	96	(46)
- Suprasternal	59	11	70	(34)
Onset - Nil	86	30	116	(56)
- URTI	22	7	29	(14)
- Foreign body	4	3	7	(3)
- 'Life event'	46	9	55	(27)

TABLE 6.5 - Clinical Features and Results of Routine Investigation of Globus Patients

		FEMALE	MALE	TOTAL (%)
Symptoms	n	158	49	207
	Dysphagia	39	7	46 (22)
	Hoarseness	70	14	84 (41)
	Pain	37	12	49 (24)
	Postnasal drip	82	14	96 (46)
	Weight - increase	35	9	44 (21)
	- decrease	15	5	20 (10)
	Heartburn - Nil	62	19	81 (39)
	- < 1/month	35	19	54 (26)
	- 1/month - 1/week	28	4	32 (15)
	- > 1/week	33	7	40 (19)
	Bowel habit abnormality	28	8	36 (17)
Past History	n	158	49	207
	Arthritis	69	19	88 (43)
	Sinusitis	55	6	61 (29)
	Psychiatric	16	7	23 (11)
Investigation	n	74	24	98
	Full blood count normal	74	24	98 (100)
	Biochemistry normal	67	22	89 (91)
	Folate/B_{12}/Thyroxine normal	72	24	96 (98)
	X-ray cervical spine - normal	33	17	50 (51)
	- degeneration	24	6	30 (31)
	- osteophytes	17	1	18 (18)
	X-ray sinuses - normal	62	19	81 (83)
	- mucosal thickening	9	5	14 (15)
	- opacification	2	0	2 (2)

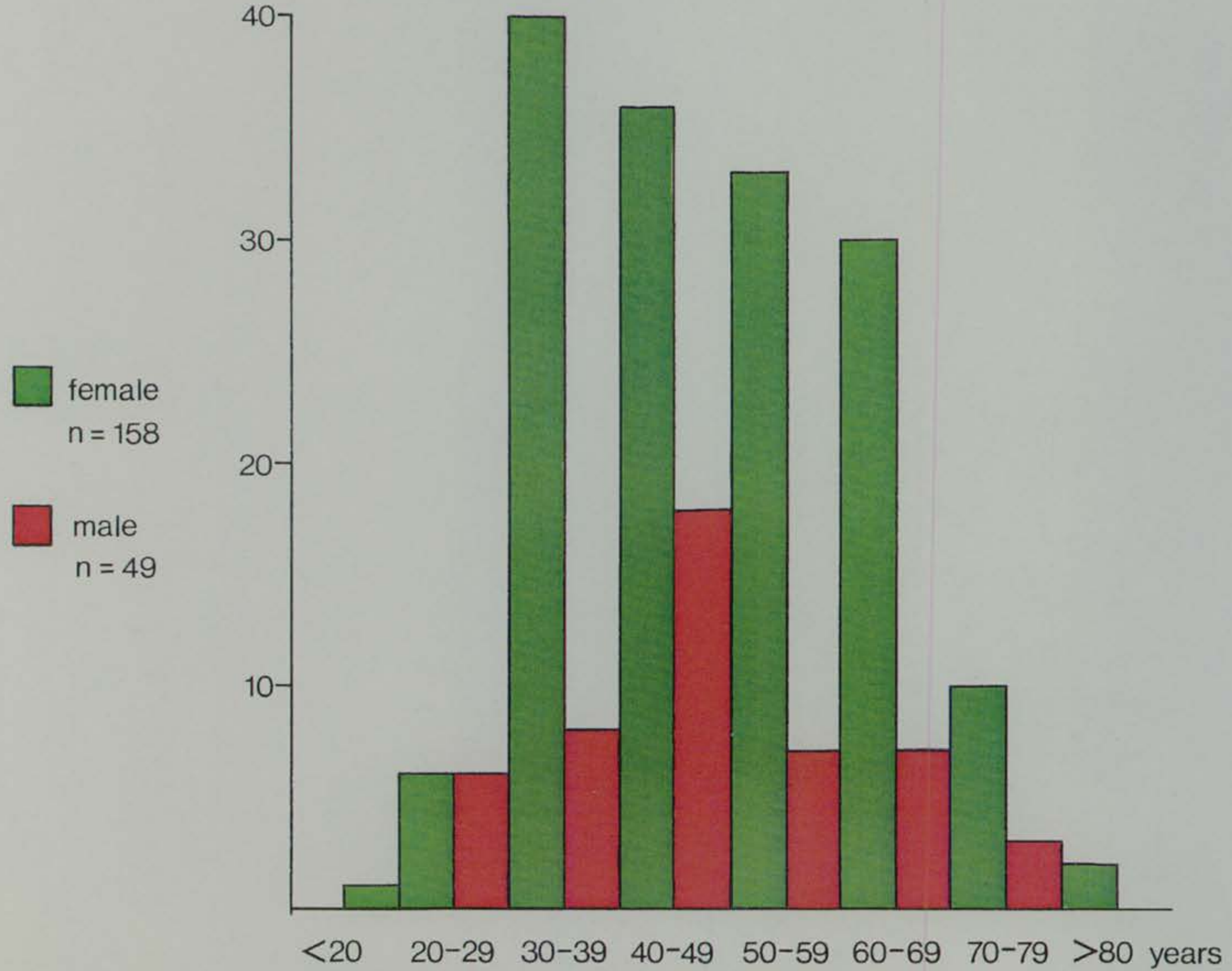


FIGURE 6.1 - Age Distribution of 207 Globus Patients

sucking it forward so that its tip was wrinkled and macerated. After many negative investigations she was convinced that amputation of the uvula would cure her globus sensation and the operation was duly performed in accordance with her wishes. Her globus sensation remained unchanged. The other surgical procedures abolished the globus of only two patients.

Results of routine investigations (Table 6.5) showed that haematological abnormalities were rare. Biochemical abnormalities detected were hypercalcaemia (in a patient who later underwent resection of a parathyroid adenoma), borderline low serum iron in four patients and mildly abnormal liver function tests in four patients. Minor degrees of spondylitis were present in almost half of the patients examined but osteophytes were prominent in only three patients. Similarly, gross opacification of the maxillary sinuses was present in just two patients, although 15% had radiological evidence of mucosal thickening.

6.2.3 Discussion

The age and sex distribution of the present large series of globus patients confirms previous reports. Clinical features such as site of the sensation, duration and frequency of associated symptoms such as heartburn are generally similar to those of other large series (Henry 1958, Malcomson 1968, Moloy and Charter 1982, Batch 1988). The similarities of the patients investigated in the present and in previous studies not only confirm that globus pharyngis is a syndrome which can be readily recognised clinically but also that the patients reported in these series do, in fact, all suffer from the same clinical condition. This is clearly important when considering a clinical entity for which there is no diagnostic test and whose confirmation still rests on the exclusion of other diseases. Despite direct enquiry, fewer than half of the patients investigated could identify a possible precipitating cause. The presence of significant 'life events' in 27% must be interpreted with caution as the figure is uncontrolled and a statistical assessment of life events requires an extensive psychological investigation. It is the author's impression and is frequently the patient's conviction that such events can precipitate the presence or the awareness of globus, not least because of the compelling temporal relationship which they often share with the onset of the condition. It is also possible that in the 17% of patients with preceding upper respiratory tract infections or foreign body impaction that the physical stimulus of mucus or mucosal irritation generated a vicious circle of swallowing or throat clearing which resulted in globus but again this may be an over-interpretation as clearly the majority of the population suffers an upper respiratory infection at least annually, yet very few subsequently attend an ENT department with globus pharyngis.

The results of this prospective study do not confirm the findings of previous small series or anecdotal reports of a high incidence of lingual tonsillitis, vitamin deficiency, osteophyte formation or sinusitis in globus. Enlarged lingual tonsils were noted in only seven patients and their reduction by cryosurgery was an effective treatment in only one patient. The incidence of minor degrees of spondylitis is similar to that in the general age-matched population (Pallis et al 1954, Irvine et al 1965). Antral mucosal thickening was present in 15% of patients, which is certainly no greater an incidence than that in the normal population. Fascenelli (1969) reported an incidence of radiological abnormality of sinus mucosa in 26% of over 400 subjects. The suggestion of Mills (1956) that globus was due to sinusitis was based on a study of only ten patients and the results of the present study of sinus X-rays in 98 consecutive globus patients suggest that any radiological sinus abnormalities were coincidental.

In conclusion, globus sensation is so common that it is all too easy to establish spurious associations with other common minor ailments. This applies not only to some of the small, selected series which have been reported but also to larger but uncontrolled series, particularly where multiple diagnostic tests have been used. Globus is associated with a heterogenous group of minor local and distant physical abnormalities, all of which are frequently present in the absence of globus sensation. Comparison of the incidence of associated abnormalities in the present series of 207 globus patients with the corresponding incidence reported in the general population has failed to demonstrate any important aetiological factor. It is possible that globus sensation may result from a wide variety of physical triggers but the clinical consistency of the syndrome over several decades and among many different centres, and the absence of globus in the majority of patients with the same physical findings tend to suggest that a common underlying factor remains to be identified.

6.3 GASTRO-OESOPHAGEAL REFLUX AND GLOBUS PHARYNGIS

6.3.1 Methods

The principal methods used to diagnose GOR were prolonged ambulatory pH monitoring and distal oesophageal biopsy. In addition, 142 patients underwent barium studies of swallowing and oesophagogastric function in both the erect and supine positions. These were video-recorded for subsequent review by Dr P L Allan, who was not informed of the results of the other investigations.

Prolonged pH monitoring was performed in 87 patients, 65 female and 22 male, who were consecutive globus clinic attenders with the exception of one female who was pregnant at presentation and two patients who declined the investigation. The method used has been described in Section 5.1.1. Results were compared with those of the 54 control subjects described in Section 5.3.2. Also studied was a group of 28 patients with endoscopic oesophagitis and acute inflammatory infiltrate and distal oesophageal biopsy. The oesophagitis, by the criteria of Monnier and Savary (1984) was Grade 1 in 13 patients and more severe in 15 patients.

Direct laryngoscopy and oesophagoscopy were performed in 107 globus patients, including 73 of the patients who had undergone pH monitoring, with biopsy of the distal oesophageal mucosa 2 cm above the squamocolumnar junction and of the interarytenoid area of the larynx. In ten consecutive patients a biopsy was also taken from the oesophageal inlet. Biopsy specimens were all examined by Dr Juan Piris, who was not aware of the results of any of the other investigations. Inflammatory cell infiltrate, basal cell hyperplasia and any increase in papillary length were recorded (Whitehead 1985).

pH monitoring data were analysed by the Mann Whitney U-test and by Pearson correlation coefficients.

6.3.2 Results

The results of video-recorded barium examinations are summarised in Table 6.6. The investigation was normal in 69% and the commonest abnormalities were GOR or hiatus hernia (11%). None of the suspected pharyngeal irregularities (8%) was confirmed endoscopically and these were, therefore, attributed to prominence of the pharyngeal venous plexus. One male patient with midoesophageal dysmotility had vigorous achalasia (see Section 6.4.2). The remainder had deficiency of the peristaltic wave in the supine position with some tertiary contractions. Only one patient was noted to have oesophagopharyngeal reflux. The other two miscellaneous findings were a degree of radiological cricopharyngeal spasm and a small traction diverticulum in the upper thoracic oesophagus.

Results of pH monitoring are listed in Table 6.7. There was no significant difference in total, upright or recumbent acid exposure times between globus patients and either control group. The median total and upright AETs in the chest pain group were slightly lower than those of the asymptomatic controls. The distribution of total AET in globus patients was somewhat different from that of controls (Figure 6.2). Of the 87 patients studied, 30 had total AETs below the first quintile of the control distribution, and 20 globus patients (23%) had a total AET greater than 10%, ie clearly outwith the working upper limit of normal for our laboratory. All three AETs were significantly greater in the group with histological oesophagitis on Mann-Whitney U test ($p < 0.00001$). There was no significant difference in total AET between smokers and non-smokers and no association of AET in globus patients or controls with age, sex or weight. Age was, however, correlated with AET in the oesophagitis group ($r = 0.61$, $p < 0.001$).

The association of heartburn and AET is shown in Figure 6.2. Although the median AET is significantly greater in patients with

TABLE 6.6 - Video Barium Findings in Globus Sensation

	MALE	FEMALE	TOTAL (%)
n	110	32	142
Normal	76	22	98 (69)
Hiatus hernia/GOR/Oesophagitis	12	4	16 (11)
Venous impression/Irregular pharynx	10	2	12 (9)
Midoesophageal dysmotility	7	2	9 (6)
Peptic ulcer	3	1	4 (3)
Miscellaneous	2	1	3 (2)

TABLE 6.7 - Percentage Time Intraoesophageal pH < 4 on Ambulatory pH Monitoring

		UPRIGHT	RECUMBENT	TOTAL
	n	Median (range)	Median (range)	Median (range)
Globus	87	5.4 (0.3-22.5)	0.2 (0-27.2)	4.2 (0.22-17.3)
Asymptomatic volunteers	34	4.4 (0.9-19.6)	0.75 (0-13.3)	3.9 (0.6-16.0)
Chest pain controls	20	2.3 (0.3-17.9)	1.5 (0-12.3)	2.5 (0.4-12.6)
Oesophagitis	28	16.5 (2.1-56.0)	12.8 (0-70.5)	17.7 (1.6-43.4)

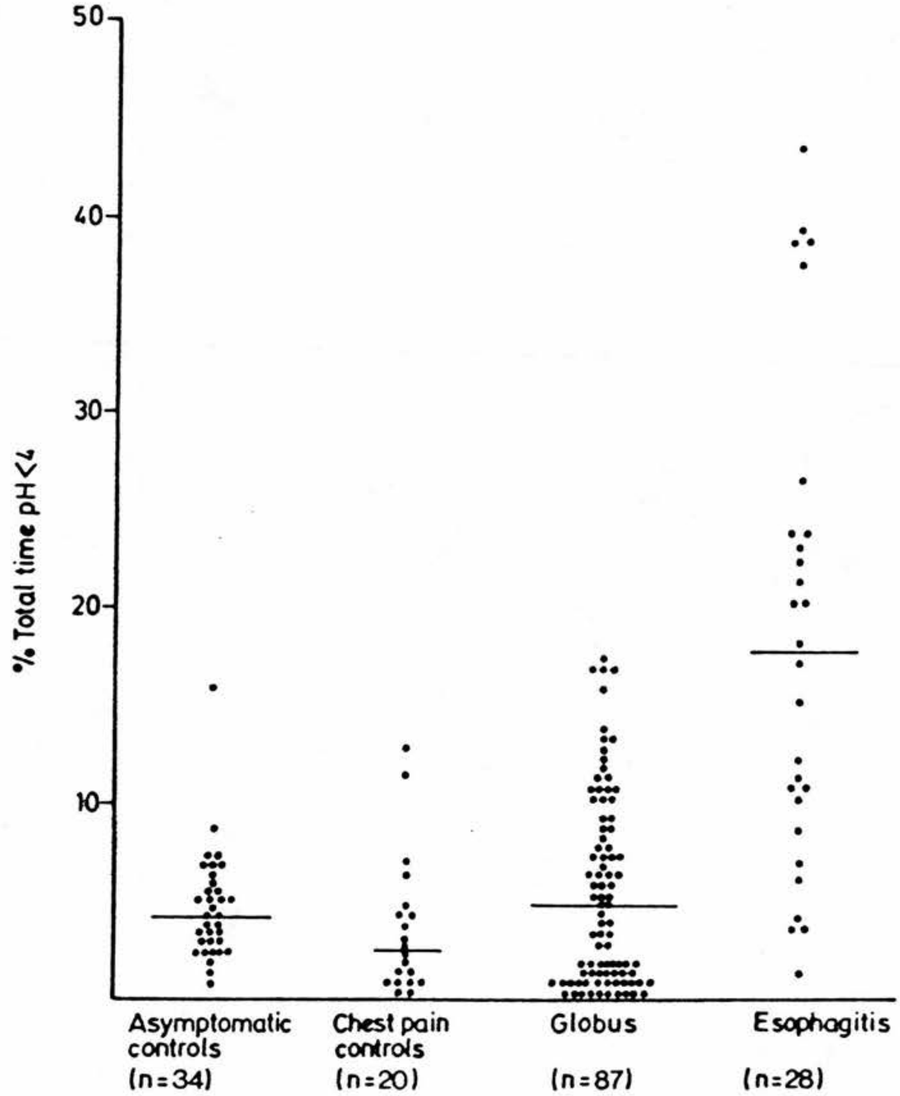


FIGURE 6.2 - Percentage Total time of Intra-oesophageal pH less than 4 in Controls, Globus Patients and Oesophagitis Patients
(Medians are indicated)

heartburn more than once per month than in patients with no heartburn ($p < 0.01$), there is clearly considerable overlap of the range of AET in the three patient groups. During pH monitoring, 56% of patients experienced no heartburn. Of the remaining 38 patients, pain episodes were not related to GOR in 20 (53%). In the 18 patients whose heartburn was sometimes observed to be reflux-associated, the mean number of heartburn episodes was 5.4, just over half of which were reflux-related.

Distal oesophageal biopsy of 107 patients showed acute inflammation with an infiltrate of polymorphonuclear leucocytes in only two patients. Three patients had a focal chronic inflammatory infiltrate thought to be of little significance; greater degrees of chronic inflammatory infiltrate were present in 15 patients. Overall, therefore, some inflammation was noted in 20 patients (18%). Epithelial basal cell hyperplasia or elongation of the rete pegs was present in 5%. Of the 73 patients undergoing both pH monitoring and oesophageal biopsy, 10 had histological evidence of inflammation. Four had total AET less than 10% and these included the three patients with only a single focus of inflammatory cells. Of the seven patients with more generalised inflammation, total AET was also abnormal in six.

None of the ten biopsy specimens from the oesophageal inlet showed evidence of heterotopic gastric mucosa. Small foci of chronic inflammatory cells were, however, observed in seven specimens, and oedema and fibrosis were present in one further biopsy. Interarytenoid changes were observed in over 30% of patients: 23% had mild chronic inflammation and 9% had epithelial changes of keratosis or parakeratosis. Of the patients with abnormal findings on laryngeal biopsy, 25% had abnormal GOR (on pH monitoring and/or distal oesophageal biopsy) and 50% were smokers.

6.3.3 Discussion

The theory that globus sensation might be due to GOR originated from the studies of Henry (1958) and Steinmann (1961) and the more extensive survey by Malcomson (1966) who found a 63% incidence of gastro-oesophageal or gastroduodenal abnormality on barium meal. These results are not supported by the present results which show radiological evidence of GOR or hiatus hernia in only 11% of 142 globus patients studied prospectively and an incidence of peptic ulceration of just 3%, despite careful analysis of video-recorded examinations. Other studies, all but one uncontrolled, using clinical assessment and acid barium techniques, showed oesophageal acid sensitivity in up to 90% of globus patients (Delahunty and Ardran 1970, Cherry et al 1970, Freeland et al 1974) but only 18% if heartburn sufferers were excluded (Mair et al 1974). Acid barium testing is now known to have a high incidence of false positive results and is inferior to prolonged oesophageal pH monitoring in the diagnosis of GOR (Richter and Castell 1982).

Heartburn occurs in 39% of the general population if appropriate inquiry is made (Thompson and Heaton 1982) and 12 patients with occasional heartburn were, therefore, included in the chest pain control group for pH monitoring. The total and upright AETs in this group were, however, slightly lower than those in the asymptomatic control group (Table 6.7 and Figure 6.1), a reflection of the prior negative tests of oesophageal function in the chest pain control group. In the present study of unselected patients with globus pharyngis, 61% complained of heartburn, although this was more often than monthly in only 34% (Figure 6.2). This might imply some support for GOR in the pathogenesis of globus but symptomatology is not a reliable indicator of oesophageal pathology. Like those of Branicki et al (1982) and Monnier and Savary (1984), the present results show no useful association of heartburn and acid exposure (Figure 6.2). Thus, the presence of heartburn per se does not establish GOR as an aetiological factor in globus. Thompson and Heaton (1982) were also unable to demonstrate any association of symptoms of globus and heartburn in the general population. Similarly, the overlap of total AET between oesophagitis patients and controls (Figure 6.3) supports the suggestion that endoscopy should be used in conjunction with pH monitoring to maximise diagnostic yield (Vitale et al 1984).

Total, upright and recumbent AETs in the 87 globus patients studied were not significantly different from those of control subjects on non-parametric testing, but such analysis cannot allow for the difference in data distribution between the patients and the controls. Thus, in respect of total AET, 23% of globus patients had an abnormal result (greater than 10%), while 34% had results below the first quintile of the control distribution. Also, 23% of globus patients had some abnormality of distal oesophageal biopsy. Of 73 patients undergoing both investigations, four (5.5%) had a total AET within the normal range but abnormal findings on distal oesophageal biopsy. In three of these, the changes were focal and thought to be insignificant phenomena of doubtful clinical relevance. Ismail-Beigi et al (1970), in a study of suction biopsies of the distal oesophagus, proposed that epithelial changes of basal cell hyperplasia and elongation of the subepithelial rete pegs were the result of GOR and Johnson et al (1978) showed that the severity of these histological findings were related to the magnitude of acid exposure on pH monitoring. It is questionable, however, whether the 5% incidence of such epithelial changes in the present series is due to abnormal GOR, as the incidence of such findings in the general population appears to be up to 19% even where biopsies are taken more than 2.5 cm from the squamocolumnar junction (Weinstein et al 1975). Some of the controversy surrounding these diagnostic criteria for GOR may be due to the problems in obtaining true perpendicular tissue sections which can be difficult even with a dissecting microscope (Hattori et al 1974) and this is a potential source of error even in the present study where substantial biopsies were taken using large cup forceps.

Even if the pH monitoring results are accepted as including a 5% incidence of false negative findings, the incidence of GOR in globus patients in this study is still under 30%. This finding supports the conclusions of the uncontrolled trials of antacid therapy in globus, which suggested the presence of a strong placebo response as results were similar in refluxers and non-refluxers (Mair et al 1974, Moloy and Charter 1982). These studies suggest that, in some patients at least, the link between globus and GOR may be no more that the casual association of common conditions. It was not possible to relate globus sensation with episodes of reflux on pH monitoring, due to the patients' awareness of the naso-oesophageal tube in the pharynx during the test. Only 21% of patients experienced reflux-related heartburn during the study and even in this group, only half of the heartburn episodes were, in fact, temporally related to a drop in pH.

Ossakow et al (1987) studied 63 patients with cervical symptoms including globus and hoarseness and reported a 68% incidence of reflux based on a positive response to the acid reflux test (gastric loading with 300 ml 0.1N HCl). Gastric acidification is known to reduce resting LOS pressure and this incidence is likely, therefore, to be a considerable over-estimate (Stacher 1985), particularly as the incidence of endoscopic abnormality was less than 10%. It is a measure of the persisting popularity of reflux as an aetiological factor in otolaryngological practice that Ossakow et al attributed not only the normal endoscopic findings but also the absence of reflux symptoms and of positive response to Bernstein testing to a reduction in mucosal sensitivity of the oesophagus rather than to the possibility that GOR may not, after all, have been of prime importance in the patients studied. The only other report of prolonged pH monitoring in globus is that of Batch (1988) who concluded that globus was reflux-related in 60% of 136 patients studied, despite a 69% incidence of normal oesophageal biopsy in those undergoing endoscopy. Also, fewer than one quarter of the patients studied were selected for investigation by pH monitoring and the upper limit of normal used was arbitrary (A J G Batch, personal communication 1988) and would be regarded by many as being unacceptably low.

There was no greater incidence of abnormal GOR in 32% of patients with abnormal findings on laryngeal biopsy. This is in keeping with the finding that reflux-related changes in the posterior laryngeal epithelium are uncommon, even in the presence of classic symptoms of so-called 'acid laryngitis' (Section 5.3). New to this study is the finding of histological changes in the upper oesophageal epithelium in eight of ten patients biopsied. It remains unclear, however, whether the mild inflammation observed in the posterior larynx and upper oesophagus is causally related to globus sensation, given that laryngeal biopsy changes were present in only 32% of patients and that the incidence in the general population of small aggregates of chronic inflammatory cells in the upper oesophagus is unknown.

The findings of the present study of a large series of unselected patients with globus sensation suggest that GOR does not explain the symptom in at least two thirds of patients. Also, patients with severe reflux seen in gastroenterological practice do not present with globus pharyngis. Thus, previous reports appear to have greatly over-estimated the importance of pathological reflux in globus sensation. Physical abnormalities such as reflux may initiate or exacerbate globus but do not explain the occurrence of this pharyngeal sensation in only a minority of sufferers, and it appears unlikely that there is a unified organic aetiology of globus. The two remaining sections of this chapter will, therefore, consider possible underlying mechanisms for the generation of globus pharyngis.

6.4 PHARYNGO-OESOPHAGEAL DYSMOTILITY IN GLOBUS PHARYNGIS

6.4.1 Methods

Initial manometric investigations of globus patients were performed with the Arndorfer catheter linked to a chart recorder according to the protocol described in Section 4.1.2. A small number of subjects at the outset of the study underwent only lower oesophageal manometry and these patients are not, therefore, considered here. The patients were otherwise consecutive attenders at the globus clinic. Studies of lower and upper oesophageal motility were performed in 82 globus patients, 13 males and 69 females, mean age 50 years (SD = 13). Results were compared with those of 13 asymptomatic volunteer controls, 10 males and three females, mean age 27 years (SD = 4). These preliminary studies were performed in conjunction with the investigations for reflux described in Section 6.3.

Later studies were carried out using the Gaeltec catheter to record UOS tonic SPT pressure and to assess pharyngo-oesophageal motility (as described in Section 4.4.1) in a further 83 globus patients, 36 males and 47 females, mean age 51 years (SD = 14). Results were compared with those of 67 control subjects, 39 males and 28 females, mean age 42 years (SD = 19, t = 3.5, $p < 0.001$). There was no significant age difference between male globus patients (mean = 50 years) and female patients (mean = 52 years). The control subjects are described fully in Section 4.4 and Section 4.6. The total UOS wet swallow complex duration, including 'E' wave descent, and the duration of UOS relaxation and after-contraction were calculated as described in Section 4.5.1. Fifty of the controls and 31 of the globus patients also underwent sleeve catheter studies of UOS tonic pressure and motility (Section 4.4.1). Both catheters were used in conjunction with the GR800 recorder.

All data were analysed by the SPSSX programme. Statistical analysis of the Arndorfer data was by unpaired Student's t-test. As the patient group was significantly older than the controls and in view of the previously demonstrated influence of age and sex on certain aspects of pharyngo-oesophageal motility, results from the Gaeltec and sleeve catheters were analysed by multiple regression analysis with subject group, age and sex.

6.4.2 Results

Results with the Arndorfer catheter are listed in Table 6.8. There is no significant difference between globus patients and controls in tonic LOS or UOS pressures on SPT. Peak UOS after-contraction pressures following dry swallows are also very similar in the two groups but there is a trend to greater UOS after-contraction pressures following wet, but not dry, swallows in the globus group (Student's $t = 1.9$, $p = 0.06$). A wide distribution of this parameter in globus patients was noted (SD = 51 mmHg). In a 30 year old male patient there was evidence of simultaneous repetitive nonpropulsive motor activity in the oesophageal body. In this patient, LOS relaxation was incomplete and a diagnosis of diffuse oesophageal spasm with possible early achalasia ('vigorous achalasia') was made. In addition to long-standing globus sensation, which had resulted in three previous negative oesophagoscopies, the patient also had complaints of episodic choking and dysphagia during consumption of solid foods.

Results with the Gaeltec catheter are listed in Table 6.9. As with the Arndorfer catheter findings, there is no significant difference on regression analysis in either tonic LOS or tonic UOS SPT pressure between the two groups. Mean peristaltic amplitude was not significantly different in globus patients and controls and mean peristaltic velocity in patients (3.7 cm/sec) was also similar to that of control subjects (3.2 cm/sec, NS). Regression analysis showed an inverse relationship of peristaltic amplitude with age ($t = -4.3$, $p < 0.0001$). Pressures were also

TABLE 6.8 - Manometric Findings in Globus Patients I: Arndorfer Catheter (pressures in mmHg)

	CONTROLS (n = 13)		GLOBUS PATIENTS (n = 82)	
	X	SD	X	SD
LOS				
- mean RPT pressure	30	16	33	14
- mean tonic SPT pressure	21	10	17	7
UOS SPT				
- maximum tonic pressure	70	19	70	29
- peak (dry swallow) pressure	127	32	126	34
Wet Swallow				
- UOS after-contraction	107	29	126^{+}	51
- pharyngeal contraction	53	21	60	24

$^{+}$ $p = 0.06$

TABLE 6.9 - Manometric findings in Globus Patients II: Gaeltec Catheter (pressures in mmHg)

	CONTROLS (n = 67)		GLOBUS PATIENTS (n = 75)	
	X	SD	X	SD
LOS				
- mean RPT pressure	19	9	23	9
- mean tonic SPT pressure	16	7	14	7
Peristaltic				
- amplitude	76	40	68	38
- velocity (cm/sec)^{o}	3.2	0.9	3.7	1.6
- duration (sec)^{o}	3.8	1.0	3.6	1.1
UOS SPT				
- mean maximum tonic pressure	37	15	40	18
- peak (dry swallow) pressure	96	31	117$^{\emptyset}$	39
Wet Swallow				
- UOS relaxation pressure	6.6	5.1	2.1^{++}	8.3
- UOS pressure at peak pharyngeal pressure^{o}	10.0	5.5	9.3	7.4
- UOS after-contraction	85	38	106^{+}	38
- pharyngeal contraction	47	29	72*	51
- time to after-contraction (secs)	2.10	0.70	1.82*	0.53
- duration (secs)	4.34	1.16	3.28**	0.93
- pharyngo-oesophageal velocity (cm/sec)	3.2	0.7	3.0	0.9

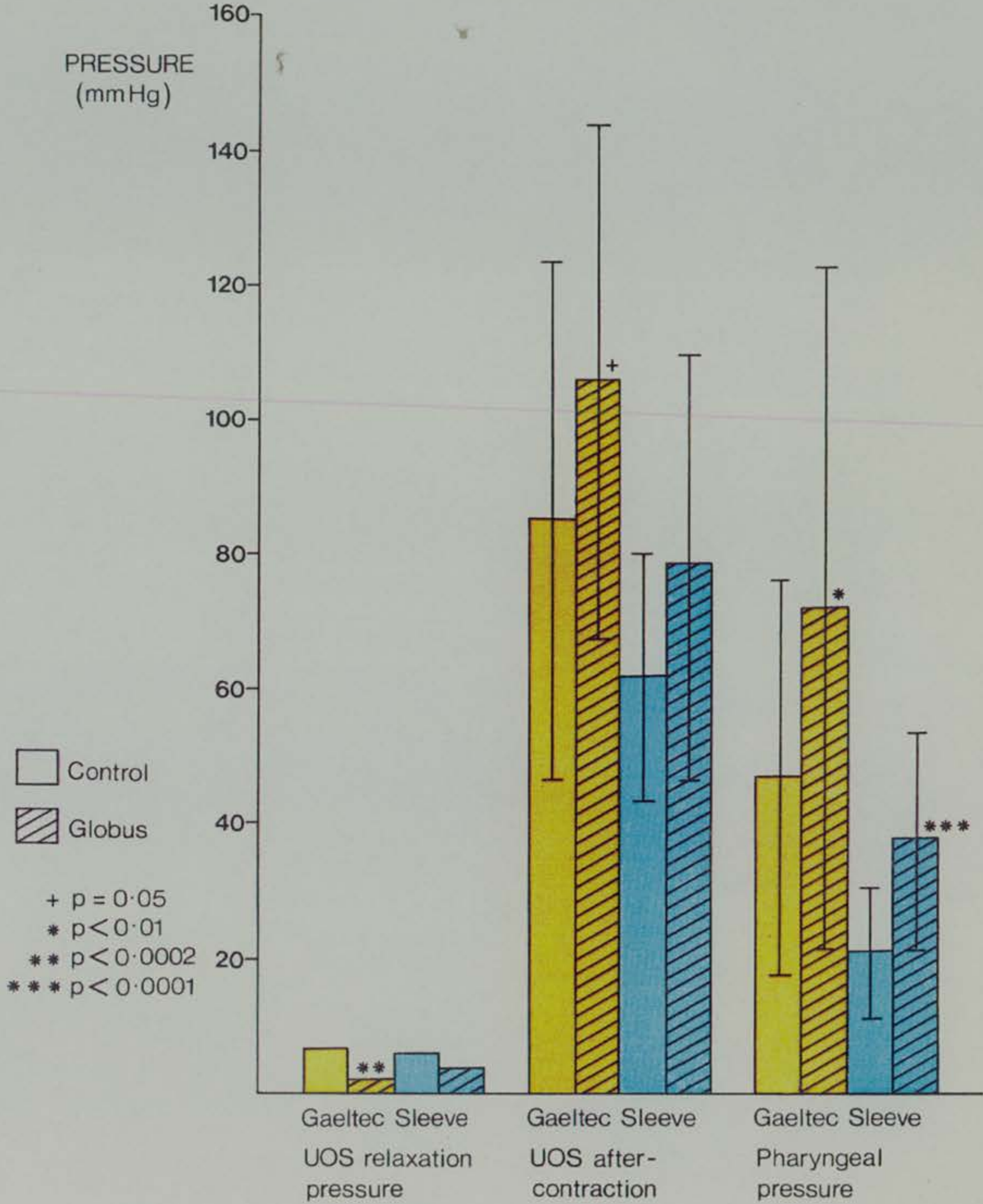
^{o} controls n = 17, globus n = 25

$^{\emptyset}$ p = 0.08, $^{+}$ $p < 0.05$, * $p < 0.01$, $^{++}$ $p < 0.0002$, ** $p < 0.0001$ on multiple regression with age and sex higher in females ($t = 2.7$, $p < 0.01$) as previously shown in the control group (Section 4.6.2) but there was no significant difference between globus patients and controls ($t = -0.5$, $p = 0.64$).

Detailed analysis of pharyngo-oesophageal swallow parameters showed several differences in contraction amplitude and swallow timing between globus patients and controls (Figure 6.3). With the Gaeltec catheter mean UOS after-contraction following dry swallows was 21 mmHg higher in globus patients than in controls (regression coefficient = $16.4 \pm$ SE 9.2, $t = 1.79$, $p = 0.08$). Analysis of wet swallows recorded with the Gaeltec catheter confirmed the trend to higher UOS after-contraction pressure in globus patients shown with the Arndorfer catheter ($t = 2.0$, $p < 0.05$). The regression coefficients for wet swallow after-contraction pressure also revealed a significantly greater pressure in females than males ($t = 2.3$, $p < 0.03$). A similar sex difference had been observed in the control group (Section 4.4.5). In female globus patients, the mean UOS after-contraction pressure (109 mmHg) was greater than that in female controls (98 mmHg), but the difference was not significant on an unpaired t-test. In male globus patients, however, the mean after-contraction pressure was almost identical to that of female globus patients (99 mmHg) and this was significantly greater than the mean after-contraction pressure in male controls (76 mmHg) on a t-test ($t = 3.2$, $p < 0.002$). The difference between male and female globus patients was not significant, however, and the inclusion of male patients as a separate variable in the regression equation showed that no significant additional weight was given to the difference between patients and controls by the male patients.

Pharyngeal contraction amplitude was also significantly greater in globus patients ($t = 2.6$, $p < 0.01$). The increase was more marked in females (mean = 82 mmHg) than in males (mean = 60 mmHg, NS on an unpaired t-test). The increase with increasing age previously observed in normal subjects was also apparent in the

FIGURE 6.3 - Pharyngeal and UOS Pressures in Globus Pharyngis



regression analysis ($t = 2.2$, $p < 0.03$). UOS minimum relaxation pressure, on the other hand, was significantly lower in globus patients of both sexes ($t = 3.9$, $p < 0.0002$). Despite the difference in minimum relaxation pressure, however, UOS relaxation pressure at the moment of peak pharyngeal contraction was very similar in the two groups. The globus group had a reduced time to peak aftercontraction ($t = 2.65$, $p < 0.01$) and the mean total UOS wet swallow complex duration was more than 1 sec shorter in globus patients ($t = 4.2$, $p < 0.0001$). The rapid, hypertonic swallow pattern observed in globus patients is represented schematically in Figure 6.4.

Results with sleeve catheter are listed in Table 6.10. As with the two other catheters, tonic UOS pressures recorded by either the sleeve catheter side-holes or by the sleeve sensor were not significantly different between globus patients and controls. The UOS wet swallow relaxation pressure was slightly lower and the UOS after-contraction pressure 16 mmHg higher in globus patients. This was not significant on regression analysis which showed that an association of age and sleeve after-contraction pressure ($t = 2.00$, $p < 0.05$) was responsible for most of the difference. The Gaeltec catheter finding of a significantly greater pharyngeal contraction amplitude in globus patients was confirmed by regression analysis of the sleeve side-hole recordings ($t = 4.8$, $p < 0.0001$).

6.4.3 Discussion

An early manometric study of globus patients proposed that UOS hypertonicity was responsible for globus sensation (Watson and Sullivan 1974). The results of the present study confirm those of several other studies which showed no difference in UOS tone between globus patients and controls (Caldarelli et al 1970, Flores et al 1981, Linsell et al 1987). Using three manometric methods in 130 globus patients and 63 controls, the present results show no evidence of UOS hypertonicity. Watson and

FIGURE 6.4 - Wet Swallow Patterns in Controls and Globus Patients

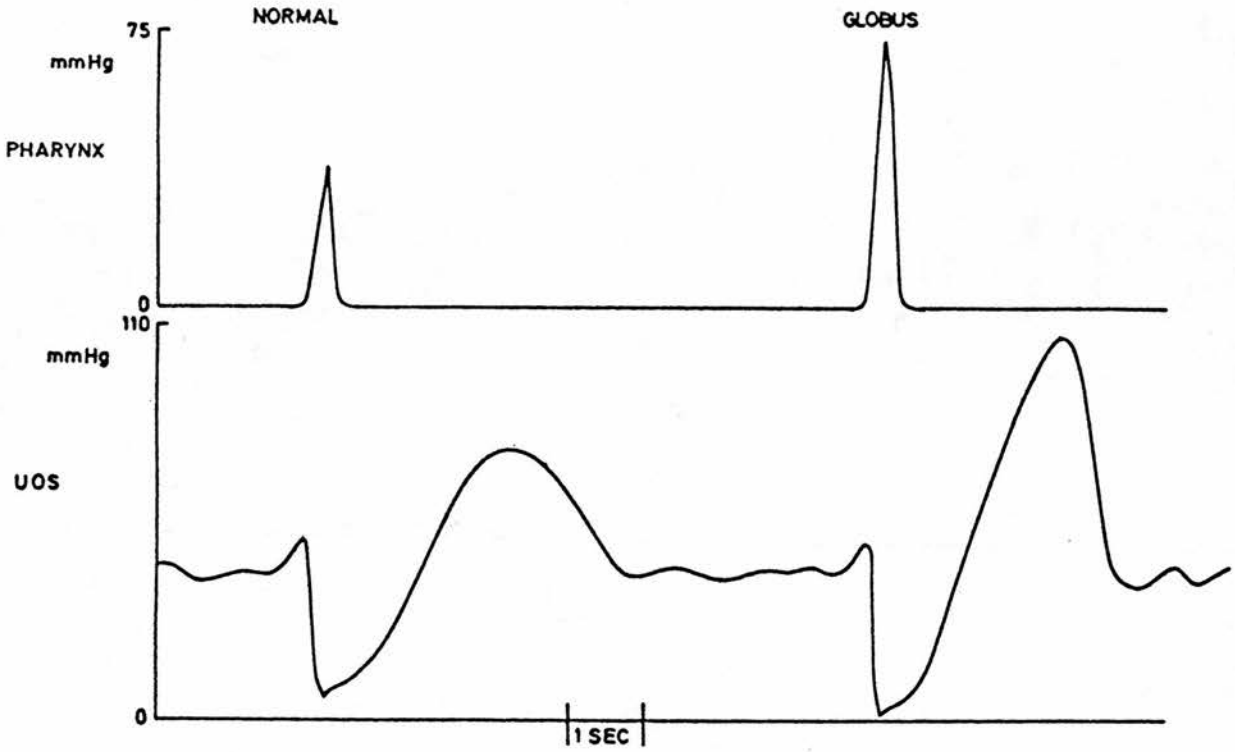


TABLE 6.10 - Manometric Findings in Globus Patients III: Sleeve Catheter (pressures in mmHg)

	CONTROLS (n = 50)		GLOBUS PATIENTS (n = 31)	
	X	SD	X	SD
UOS SPT Tonic Pressure				
- mean side-hole	53	23	55	30
- sleeve sensor	83	32	80	43
Wet Swallow Pressures				
- UOS relaxation	5.9	7.2	3.5	9.9
- UOS after-contraction	62	18	78	32
- pharyngeal contraction	21	10	38**	16

** $p < 0.0001$

Sullivan (1974) recorded unusually high UOS pressures in both globus patients and in the control group, whose heterogeneity has been discussed (Section 3.1). There appears, therefore, to be a considerable weight of evidence that resting tonic UOS pressure is normal in globus patients. It remains possible that UOS pressure may increase transiently during stress in globus patients (Cook et al 1987). Undergoing manometric investigation is, however, likely to be an equally stressful stimulus for both control subjects and patients and it seems unlikely that significant differences of stress-responsiveness of the UOS between globus patients and controls could be demonstrated manometrically. As with pH monitoring studies, the awareness of naso-oesophageal intubation is maximal in the pharynx, making it impossible to assess globus patients' habitual foreign-body sensation with any accuracy during manometry. Nonetheless, despite the suggestion that stress-induced increases in tonic UOS pressure might be a cause of globus sensation, Cook et al found that stress-induced increases in UOS tone were asymptomatic in normal subjects.

Cohen (1973) claimed that a wide variety of oesophageal motility disorders, including achalasia and diffuse oesophageal spasm could give rise to globus sensation and Flores et al (1981) were the first to demonstrate disordered midoesophageal dysmotility in globus, although no control data were published in their report. Evidence for abnormal motility in the oesophageal body was found by Linsell et al (1987) using a Gaeltec catheter in four of 18 globus patients. The present results indicate that mean peristaltic amplitude and velocity are normal in the large group of unselected globus patients studied. Only one patient had definite evidence of a midoesophageal motility disorder (vigorous achalasia) and, by the time of his referral to the globus clinic, he had developed additional symptoms of choking and episodic dysphagia for solid foods.

Detailed analysis of pharyngo-oesophageal motility during water swallows has revealed significant differences between globus patients and controls. An increased UOS after-contraction amplitude was observed in globus patients with all three catheters, although the difference was significant only for the Gaeltec catheter measurements (Table 6.9 and Figure 6.3), a reflection of the greater pressure rise rate with this method. The finding of a similar trend with both the Arndorfer and sleeve catheters (Table 6.8 and 6.10) adds support to the validity of the observation. Pharyngeal contraction amplitude measurements were also greater in globus with all three recording methods and the difference was highly significant for both the sleeve and the Gaeltec catheters. The low pharyngeal contraction amplitudes in control subjects in the present study has already been discussed (Section 4.4.7). There is nothing to suggest, however, that any alteration in performance or measurement methods contributed to the large difference in pharyngeal pressures between controls and globus patients as the controls and patients were studied concurrently. Although pharyngeal contraction amplitude increases with age, the use of regression analysis to allow for the age difference between patients and controls confirmed the presence of abnormally high pharyngeal pressures in patients of both sexes with globus pharyngis. Globus patients' swallows may, therefore, be termed 'hypertonic' in respect of both pharyngeal and UOS aftercontractions. Their swallows may also be described as 'rapid' in view of the associated reduction in time from the onset of UOS relaxation to peak after-contraction and to the end of the UOS swallow complex.

The typical rapid, hypertonic swallow of the globus patient (Figure 6.4) does not appear to be a response to incomplete UOS relaxation. With both the Gaeltec and sleeve catheters, the mean minimum UOS pressure during wet swallows was in fact lower in the globus group. The mean relaxation pressure of 2.1 mmHg recorded with the Gaeltec catheter in the globus patients (Table 6.9) may simply have been due to greater sphincter-on-catheter movement in response to the rapid, hypertonic deglutition pattern. In some patients, the three-sensor level of the Gaeltec catheter may have slipped down into the cervical oesophagus. This early decrease in UOS pressure might explain the absence of any difference in UOS relaxation pressure at the time of peak pharyngeal contraction amplitude between globus patients and controls. The method of positioning the sleeve catheter - with the upper end of the sleeve sensor at the level of maximum UOS tonic pressure - might also have given rise to such an artifact (Table 6.10). With both methods, relaxation pressures were widely distributed, particularly in the globus group (SD = 9.9 mmHg, Gaeltec and 8.9 mmHg sleeve). At least some of this intersubject variation is likely to be due to catheter movement. Accurate recording of UOS relaxation remains the most technically difficult and is the least reproducible measurement of UOS manometry (Section 4.4.7). All that can be said of the present data is that they yield no evidence of incomplete UOS relaxation in globus patients.

As discussed previously (Section 3.1), there have been some radiological studies in globus patients suggesting abnormalities of epiglottic movement (Welin 1939, Curtis and Cruess 1984), of pharyngeal peristalsis (Hannig et al 1987) or of inferior constrictor function (Gray 1983). The only manometric report of swallow patterns was the early study by Caldarelli et al (1970) who used a triple-lumen water-filled system. The principal conclusion on swallow patterns was that the spread of values of, for example, UOS after-contraction was less in globus patients than in controls, although only 10 globus patients and six controls were studied. Nonetheless, it is interesting that there was a tendency for globus patients to have reduced duration of UOS relaxation, as in the present study, where the mean time from the onset of relaxation to the peak after-contraction was significantly lower in globus patients (Table 6.9).

It is clear that Cook et al (1987) were correct in suggesting that detailed examination of UOS function in globus patients might yield interesting results, but what is the significance of these motor disorders? The pharyngo-oesophageal dysmotility may contribute to the perceived difficulty in swallowing in the absence of true obstruction to the passage of food which is experienced by 22% of globus patients (Table 6.5) but the origin of the dysmotility remains unclear. Given that transient forms of globus sensation are extremely common in the general population (Thompson and Heaton 1982), the concept of globus pharyngis as merely the sensory component of a primary motor disorder appears rather unlikely, although the demonstration of a concomitant motor abnormality has implications for the psychological classification of globus as its discovery would support the inclusion of globus among conversion disorders (Diagnostic and Statistical Manual 1980).

Mean pharyngeal pressure, which shows no sex difference in normal subjects, was significantly increased in patients of both sexes, moreso in females than males although the difference was not significant. The abnormally high UOS after-contraction pressures in globus patients are of particular interest because there is no explanation for the excess of female patients with clinical forms of globus, other than the propensity of females to minor psychological abnormalities. The male globus patients in the present series had a mean after-contraction pressure similar to that of healthy females, ie an increase of 22 mmHg compared with healthy males, whereas female patients showed an increase of 12 mmHg in mean pressure compared with healthy females. If increased wet swallow UOS after-contraction pressure is associated with globus, then the significantly greater after-contraction in normal females (Section 4.4) may contribute to the observed sex difference in the incidence of globus (Figure 6.1), ie normal females may be 'physiologically closer' to the development of globus sensation than are healthy males and in females a smaller increment in UOS contraction amplitude may be sufficient to generate the symptom. On the other hand, dry swallow UOS contraction amplitude, although greater, was not significantly increased in the patient group, yet the symptom is well-known to be perceived maximally during dry swallows.

It is also possible that the rapid, hypertonic swallow pattern is a secondary elaboration in response to the feeling of something in the throat, ie the patient makes more forceful swallowing movements in an attempt to swallow 'past the lump'. On the other hand, the swallow pattern is clearly different from that observed during bread swallows (Section 4.6.2) where there is also an increase in pharyngeal and UOS contraction amplitude, but where the duration of swallow events is increased rather than reduced as in the globus group. It may be, therefore, that the observed pharyngo-oesophageal dysmotility contributes to the generation of globus sensation. In some patients this may occur in association with a minor organic trigger such as post-nasal catarrh which, in susceptible individuals, may lead to a vicious circle of rapid, hypertonic swallows. This is akin to the cycle of 'strain swallows' proposed by Gray (1983), although Gray reported no evidence to support his hypothesis.

Whether pharyngo-oesophageal dysmotility is a response to globus or contributes to its generation, the same basic question remains: what makes an individual liable to develop severe, persistent forms of an otherwise transient phenomenon of little consequence? Previous suggestions include abnormal autonomic activity secondary to stress anxiety (Cook et al 1987) and the final section of this chapter is addressed to the psychological aspects of the globus symptom.

6.5 PSYCHOLOGICAL ASPECTS OF THE GLOBUS SYMPTOM

The aims of the study were to return to the earliest ideas of the aetiology of globus in an attempt to establish whether or not there was any scientific basis for the centuries-old concept of globus as a manifestation of psychological distress.

6.5.1 Methods

A preliminary study was performed in 46 consecutive patients, nine males and 37 females, attending the globus clinic. The mean age of the male patients was 43 years (SD = 12) and of females was 47 years (SD = 11). The patients were given two self-scoring questionnaires - the Eysenck Personality Inventory (Eysenck and Eysenck 1964) and the 60 item version of General Health Questionnaire (Goldberg 1972). The EPI yields neuroticism, extraversion and lie scores. EPI results were compared with those of published age and sex-matched normals (Eysenck and Eysenck 1964) using Student's unpaired t-test.

Later studies were performed in 121 globus patients, 30 males and 91 females, in conjunction with several honours students from the department of psychology (see page iv) who attended the globus clinic to administer the questionnaires. The mean age of the male patients was 47 years (SD = 12) and of the females 50 years (SD = 13). For all questionnaires except the Crown Crisp Experiential Index which had appropriate age-matched control data, 66 control ENT outpatients (42 females and 24 males) were recruited. Controls had a clear physical ENT disorder (deafness, nasal fracture, sinusitis, etc). The mean age of females was 47 years (SD = 14) and of males was 43 years (SD = 14), ie not significantly different from the globus patients. All patients and controls completed the Eysenck Personality Questionnaire (Eysenck and Eysenck 1975). Other questionnaires were allocated randomly to globus patients and controls. Subjects were given instructions regarding the completion of the questionnaires and completed them without time pressure in a quiet room.

The EPQ is a 90 item questionnaire which gives scores on the following personality traits: neuroticism, extraversion, psychoticism and lie. The first are generally agreed to be the three most important personality dimensions. The lie scale is an estimate of the degree to which a subject is giving socially desirable answers. The CCEI (Crown and Crisp 1979) was used to assess 71 patients, 19 males and 52 females. This 48 item questionnaire quantifies symptoms and traits relevant to the standard categories of psychoneurotic illness and personality disorder. It gathers the same information as would be obtained in a short psychiatric interview. Scores are obtained on the following scales: free floating anxiety (FFA), phobia (PHO) obsessionality (OBS), somatisation (SOM), depression (DEP) and hysteria (HYS). The 60 item version of the GHQ was used in 79 patients, 18 males and 61 females and in 58 controls, 16 males and 42 females. This is a well-established method for the detection of covert non-psychotic psychiatric disturbance among general medical patients. A GHQ score of greater than 12 is a predictor of occult psychiatric morbidity. The Hysteroid Obsessoid Questionnaire (Caine and Hope 1967) was used in 50 patients, 12 males and 38 females and in 54 controls, 16 male and 38 female. This 48 item test indexes the two opposing trait constellations found in neurotic patients. High scores indicate hysteroid traits while low scores indicate obsessoid traits.

Data were analysed by Student's unpaired t-test and by Pearson correlation coefficients. The z statistic was used to analyse CCEI scores. This figure is the number of SD units by which a sample mean differs from a population mean and can, therefore, be used to compare published normal ranges (in the absence of raw data) with results from an experimental sample. Dr Ian Deary performed the statistical analysis of the psychometric tests. Selected parameters were subsequently joined to the SPSSX files of the manometric and pH data by the author to assess any possible association of psychological and physical variables in globus patients.

6.5.2 Results

EPI scores in the preliminary group of 46 subjects studied are listed in Table 6.11. Compared with published normals, female globus patients had significantly increased neuroticism scores ($p < 0.001$), while male patients had low neuroticism scores. Extraversion scores were also similar to normals in male patients but females were significantly more introverted ($p < 0.01$). The higher lie scores in females may have been due to their slightly older age: the lie score was positively correlated with age ($r = 0.41$, $p < 0.01$). The GHQ score was greater than 12 in 14 patients, one male and 13 females. The single male in this group was the patient with manometric evidence of vigorous achalasia (see Section 6.4.2). The mean neuroticism score was significantly greater in high GHQ scorers ($X = 14.1$, $SD = 3.8$), compared with those whose GHQ scores were 12 or less ($X = 9.6$, $SD = 5.4$, $p < 0.01$), an association confirmed by Pearson correlation ($r = 0.45$, $p < 0.01$).

Results of the EPQ, GHQ and HOQ in the larger series of patients studied subsequently are listed in Table 6.12. Female globus patients were significantly more introverted than ENT controls ($t = 2.81$, $p < 0.01$), who were similar to published age-matched normals (Eysenck and Eysenck 1975). Male globus patients were similar to ENT controls and both groups were similar to published age-matched normals. Mean EPQ neuroticism scores in female globus patients were not significantly greater than those of female ENT controls. Male globus patients had similar neuroticism scores to those of controls. Both male and female globus groups had significantly increased lie scores ($t = 2.10$, $p < 0.05$ male; $t = 2.72$, $p < 0.01$ female). As in the previous sample of 46 patients, GHQ scores were significantly greater in female globus patients than in controls ($t = 2.39$, $p < 0.02$). Male

TABLE 6.11 - Results from the EPI in 46 Globus Patients

	MALE NORMALS (n = 93)		MALE GLOBUS (n = 9)		FEMALE NORMALS (n = 24)		FEMALE GLOBUS (n = 37)	
	X	SD	X	SD	X	SD	X	SD
Extraversion	11.3	4.6	12.2	4.8	12.2	4.8	10.1*	4.5
Neuroticism	8.9	4.6	5.9*	4.4	7.9	5.4	12.3**	4.8
Lie			2.7	1.6			4.2	2.2

* $p < 0.01$, ** $p < 0.001$

TABLE 6.12 - Results from the EPQ, GHQ and HOQ in Globus Patients and ENT Outpatient Controls

	MALE CONTROLS		MALE GLOBUS		FEMALE CONTROLS		FEMALE GLOBUS	
	X	SD	X	SD	X	SD	X	SD
Age	43	14	47	12	48	14	50	13
EPQ								
- Extraversion	12.2	4.9	11.2	4.3	12.7	5.2	10.1*	4.8
- Neuroticism	8.9	5.4	8.2	4.5	11.5	5.7	12.7	5.6
- Psychoticism	2.2	1.4	2.9	3.8	1.8	1.8	2.4	3.1
- Lie	7.3	5.0	10.1^{+}	4.6	9.4	5.2	12.0*	4.5
GHQ	5.2	8.2	7.4	7.9	4.7	6.0	9.0^{++}	11.9
HOQ	19.9	5.3	21.4	5.4	22.7	6.4	20.8	5.7

$^{+}$ $p < 0.05$, $^{++}$ $p < 0.02$, * $p < 0.01$

globus and control GHQ scores were similar. There was no significant difference in HOQ scores between globus patients and controls.

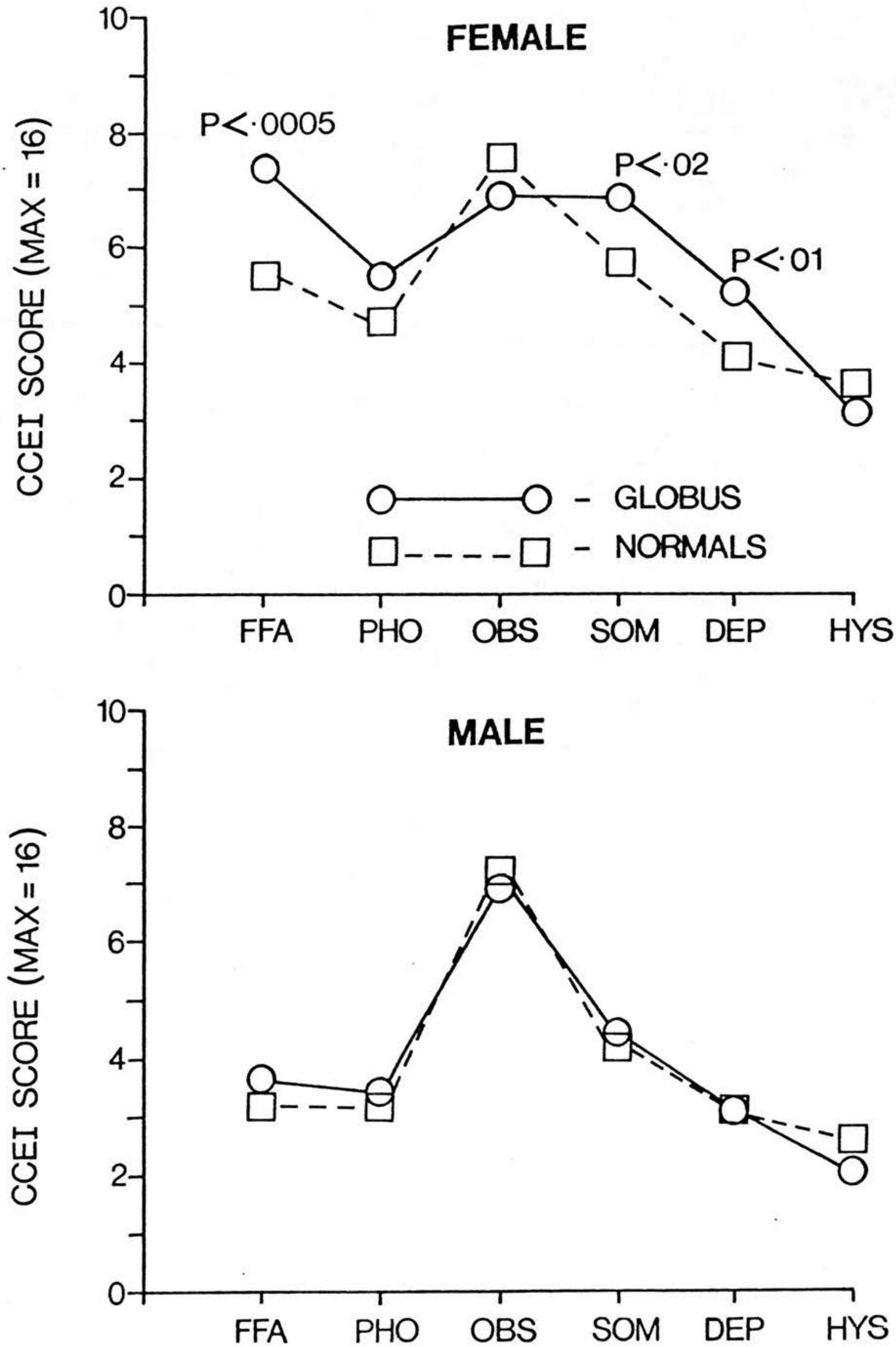
The CCEI data are summarised in Figure 6.5. On all subscales, male globus patients are similar to those of published controls recruited from general practice (Crown and Crisp 1979). Female globus patients differed significantly from controls on three subscales - free floating anxiety ($z = 3.49$, $p < 0.0005$), depression ($z = 3.11$, $p < 0.01$) and somatic concern ($z = 2.45$, $p < 0.02$).

An attempt was then made to correlate psychological parameters with the abnormal manometric parameters identified in Section 6.4. Unfortunately, due to the evolving nature of both the physical and the psychological investigations, the numbers available for such correlations were small. Forty-two subjects had undergone psychometric evaluation by the EPQ and manometric study with the Arndorfer catheter. There was no correlation of wet swallow UOS after-contraction with scores of either neuroticism ($r = 0.18$) or extraversion ($r = 0.08$). In the 30 subjects undergoing EPQ and CCEI evaluation and manometric study with the Gaeltec catheter, there was no significant correlation of any wet swallow parameter with any of the psychological variables. Correlation of GHQ scores with total AET (Section 6.3) in 48 globus patients was weakly positive ($r = 0.32$, $p < 0.05$). There was no association of AET with EPQ neuroticism scores in 47 females ($r = 0.11$) or in 56 patients of both sexes ($r = 0.06$) nor of AET with extraversion scores in either females ($r = 0.23$) or in the group as a whole ($r = 0.20$).

6.5.3 Discussion

This is the largest psychological study of globus pharyngis to date, which is perhaps surprising in view of the high incidence of globus and the long-held belief that it may have a 'hysterical' basis. In recent years, however, most globus research has

FIGURE 6.5 - CCEI Scores in Females and Males with Globus Sensation. FFA = free floating anxiety, PHO = phobic anxiety, OBS = obsessionality, SOM = somatic concern, DEP = depression, HYS = hysteroid



been directed to possible organic theories probably because patients are nowadays usually referred to otolaryngologists rather than to psychiatrists (Anonymous 1989). The preliminary findings indicated a marked sex difference, with females emerging as neurotic introverts while males appeared to be stable ambiverts compared with published controls. Study of a further 121 patients confirmed the introversion of females with globus. The mean neuroticism score of 90 females on EPQ testing was greater than that of ENT controls but the difference in this larger group was not significant. Interestingly, both males and females had high EPQ lie scores: high lie scores often indicate a desire to 'fake good' and are associated with artificially low neuroticism scores (Eysenck and Eysenck 1975). Female patients were also shown to have higher GHQ scores. The GHQ detects patients whose otherwise inexplicable somatic symptoms are accompanied by an affective disturbance (principally affective neurosis) that has not been presented to the physician. An association of anxiety and total scores has been demonstrated in a scaled version of the GHQ (Goldberg and Hillier 1979) and in the present series free floating anxiety on the CCEI was also significantly greater in female patients than in controls. A higher threshold of positivity has been recommended in the presence of physical illness (Goldberg 1986) and this might explain the weakly positive correlation of GHQ scores with AET and the high GHQ score in the male patient with vigorous achalasia. Alternatively, the presence of psychological disturbance may have contributed to both the globus sensation and the oesophageal dysmotility in this patient.

Is globus hystericus? Eysenck's original study of 700 soldiers suggested that conversion hysteria had a high extraversion loading but the 'E' factor used was unsatisfactory and there were no normal controls (Eysenck 1944). Hildebrand (1958) found conversion hysterics to be high scorers on a neuroticism dimension but intermediate between normals and dysthymics on extraversion. Eysenck has claimed more recently that hysterics are neurotic ambiverts but there is little evidence for this except for one inadequately reported study (Bolardos 1964). Moss and McEvedy (1966) found small, inconsistent differences in extraversion scores of schoolgirls with hysterical overbreathing, while other studies show no difference between conversion disorder and dysthymic disorder, ie those neuroses associated with high neuroticism and low extraversion scores (Sigal et al 1958, Eysenck 1962, McGuire et al 1963, Ingham and Robinson 1964, McEvedy et al 1966, Wilson-Barnett and Trimble 1985). The preliminary results of the present study indicated that female globus patients also fell into the dysthymic quadrant of Eysenck's personality traits, and were, therefore, not incompatible with the theory of conversion disorder in globus. In the larger sample studied with the EPQ, however, the neuroticism scores in female patients were not significantly greater than that of ENT controls.

Findings with the CCEI indicate that female globus patients are distinguished from general practice controls by their high levels of general anxiety, their low mood and their frequency of somatic complaints. The use of the same inventory in 105 globus patients was reported to show that scores were greater than general practice controls, less than psychoneurotic patients and little different from ENT controls, although male and female scores were not analysed separately (Batch 1988). The high free floating anxiety, depression and somatic concern scores may not have achieved significantly greater levels than those of the ENT controls as the latter were a retrospective control group studied by Weir and Stephens (1976) which was not age-matched and whose largest diagnostic subgroup was a vasomotor rhinitis cohort who tended to have high free-floating anxiety and somatic concern scores.

The conclusion from the present study is that psychological factors are important in globus. At least a substantial minority of the female patients are psychologically disturbed. Into which psychiatric classification does the disorder fall? The GHQ and CCEI anxiety and depression scores point to an anxiety-related disorder or to a mild reactive-type depression. The hypothesis that low mood and anxiety are manifest in the reporting of globus as a distressing physical symptom is based not only on the the CCEI findings, which include increased somatic concern but also on the significantly greater introversion scores in female globus patients. Introverts have a greater sensitivity to incoming stimuli and a greater reaction to discomfort (Eysenck and Eysenck 1985).

Analysis of the HOQ results showed no greater scores on this inventory of hysteroid traits in globus patients than in ENT controls or published normals (Caine and Hope 1967). There was also no increase in hysteroid traits in patients of either sex on CCEI testing. In a study of 79 patients with well-defined neurological manifestations of hysteria, however, Wilson-Barnett and Trimble (1985) found no increase in HOQ scores, and also demonstrated affective disturbance (notably depression) together with a trend towards introversion on EPI testing. The absence of hysteroid personality traits does not, therefore, exclude the possibility that globus is a conversion disorder, particularly in view of the presence of mood alterations and Eysenck scores in female globus patients similar to those in patients with gross neurological manifestations of hysteria. Both groups of patients may be judged to suffer from 'somatisation', ie 'a tendency to experience psychological distress in the form of somatic symptoms and to seek medical help for them' (Lipowski 1987). The finding by Othmer and DeSousa (1985) that globus was the fourth most discriminating symptom of conversion disorder also supports the classification of globus in this more specific diagnostic category, as does the demonstration of motor abnormalities (Section 6.4).

In the lower oesophagus, contraction abnormalities have been associated with findings of anxiety, somatisation and depression in patients with chest pain. As with the findings of pharyngo-oesophageal dysmotility and similar psychological features in the present study of globus patients, the significance of the association remains unclear. The depression, anxiety, somatic concern and increased stimulus sensitivity of female globus patients may exacerbate the globus sensation, perhaps by a vicious circle of hypertonic swallowing (as described in Section 6.4). Although numbers available for study were small, however, there was no evidence of the correlation of psychological and manometric parameters which might have been expected if this interaction were indeed the mechanism of generation of globus sensation. The lack of manometric improvement when symptomatic contraction abnormalities were successfully treated with low-dose antidepressant was interpreted by Clouse et al (1987) as showing a primary effect on symptom-reporting rather than the occurrence of symptoms. Such findings in the oesophageal body suggest that the interaction of psychological and somatic factors in the generation of physical symptoms may be very complex and that it is simplistic to anticipate a direct correlation of personality traits with parameters of visceral motor function. Globus, like many other physical symptoms has a 'pyramidal' incidence: at the foot of the pyramid are the 45% of the general population who accept the symptom as a transient concomitant of sadness. Others appear to experience more severe forms, but derive adequate reassurance either from their general practitioner, or from friends. At the top of the pyramid are those whose symptom is so severe that it results in hospital attendance. Similarly, the generation of the symptom may be regarded as operating on four levels: the first is the absolute amount of sensory stimulation, which is almost impossible to quantify. The second is the patient's awareness of the sensation, which is clearly subject to psychological influences and which may result in the third level of symptom-generation by a combination of increased dry swallow frequency and hypertonic swallow patterns. The fourth is the patient's symptom-reporting habits, which are dependent not only on psychological but probably also on cultural variables, both of which may contribute to the establised sex incidence of clinical forms of globus pharyngis. It seems likely that the wide variety of physical and psychological abnormalities which have been described in this chapter act as contributory factors which either initiate or exacerbate globus sensation. The pharyngo-oesophageal dysmotility (Section 6.4) may also be a causal phenomenon in terms of both the sex incidence and of 'symptom selection' and may explain why certain anxious introverts develop globus rather than, for example, tinnitus, headache, or irritable bowel syndrome.

Patients with globus attend hospital for two principal reasons. The first is for further reassurance that there is no (cancerous) lump present in the throat, and such reassurance frequently reduces or abolishes the sensation, or at least the hospital attendance. For many patients, however, the primary aim is to get rid of what has become a distressing symptom. Such patients are often well aware of the psychological aspects of the symptom ("Could it be nerves, doctor?" is a frequent refrain in the globus clinic). Although there is a report of the successful use of antidepressant therapy in globus (Brown et al 1986), only three patients were studied and all had clinical evidence of concomitant depression. The placebo response to antidepressants in conditions as disparate as tinnitus (Mihail et al 1988) and oesophageal dysmotility (Clouse et al 1987) is considerable. No treatment should be advocated for globus while placebo-controlled trials are lacking because of the rate of spontaneous resolution and the placebo response to therapy (Moloy and Charter 1982). Antidepressant therapy has been shown to be of benefit in functional somatic symptoms (Kellner 1985) and in panic attacks which can be a concomitant of globus (Bishop and Riley 1988). Recent evidence that antidepressant therapy is also effective in mild reactive-type depression (Paykel et al 1988) suggests that there is a place for such a trial in globus patients, even where clinical depression is absent, and a placebo-controlled trial of amitriptyline therapy is now in progress in the globus clinic.

7. ABNORMAL PHARYNGO-OESOPHAGEAL MOTILITY

7.1 THE EFFECT OF IRRADIATION ON PHARYNGO-OESOPHAGEAL MOTILITY

It has been shown that pelvic irradiation produces alterations in anal canal resting pressure (Varma et al 1986) but the effects of laryngeal irradiation on UOS function are unknown. The UOS receives the full radiation dose during external beam radiotherapy to the adjacent larynx. The aim of this study was to determine the effects, if any, of radical laryngeal radiotherapy on pharyngo-eoesophageal motility

7.1.1 <u>Methods</u>

Nineteen patients were recruited from the combined ENT/radiation oncology clinic, Royal Infirmary, Edinburgh. All had received laryngeal irradiation for T_1 to T_3 N_0 glottic cancer (UICC, 1987) at least 12 months prior to the study and were clinically disease-free. Any patient in this category was invited to enter the study and the only patients excluded were those who declined to be investigated and those who had subsequently undergone surgery for recurrent disease. The patients comprised 17 males and two females, aged 49 to 85 years (mean = 65 years), of whom nine were current cigarette smokers. The case notes of each patient were reviewed. All had undergone primary irradiation of the larynx to a central dose of 52.5 to 55.7Gy in 20 fractions over four weeks. The patients were treated by small parallel opposed wedged fields (5 x 5 cm) centred on the vocal cords and extending from the anterior surface of the neck to the anterior surface of the vertebral bodies. No patient had required whole-neck irradiation as all were free from nodal disease at presentation. The time interval following treatment was 13 to 71 months (mean = 35 months). In nine, the tumour had been stage T_{1a} or T_{1b}, in nine stage T_2 and one patient had had a T_3 lesion. None had a history of intercurrent disease or medication likely to influence results.

All patients underwent the modified manometric protocol used in the older healthy volunteers (Section 4.6.1). Results were compared with those in 23 of the healthy volunteers (Chapter 4) who were aged 49 years or over, of whom five were cigarette smokers. The control group comprised 13 males and 10 females aged 49 to 77 years (mean = 65 years, ie not significantly different from patients on an unpaired t-test). Data analysis was by the Mann-Whitney U test, by Spearman rank correlation and by multiple regression analysis of results with diagnostic group, age, sex and cigarette smoking.

7.1.2 Results

Only one of the irradiated group complained of mild symptomatic dysphagia. This dated from the time of therapy but was not sufficient to induce weight loss. The incidence of heartburn was similar in the two groups of subjects: three of the patients and seven control subjects had heartburn less than monthly; four of the patients and two of the controls experienced heartburn more than once per month.

There was no significant difference in tonic LOS RPT or SPT pressure nor in peristaltic amplitude or velocity between the two groups. Regression analysis showed a trend, however, to an increase in the duration of the peristaltic wave ($t = 2.0$, $p = 0.06$). Four patients had mean maximum tonic UOS pressures of 13 mmHg or less and mean maximum tonic UOS pressure was marginally lower in patients (27 ± 11 mmHg) than in controls (33 ± 14 mmHg) but the difference was not significant on either non-parametric or regression analysis. Similarly, there was no difference in any of the other parameters of UOS tone (UOS RPT, mean tonic pressure, greatest single-channel maximum pressure or pressure/length ratio) between the two groups.

Two patients appeared to have double-peaked pharyngeal waves but only two parameters of pharyngo-oesophageal motility during water or bread swallows were significantly different between controls and irradiated patients. The amplitude of water swallow UOS after-contraction was lower in patients (77 ± 44 mmHg) than in controls (102 ± 50 mmHg), $z = -2.0$, $p = 0.05$. Regression analysis showed, however, that this was due to the small number of females (two) in the patient group compared with the females in the control group as wet swallow UOS after-contraction pressure tends to be greater in females (Section 4.4.5). The regression coefficient for the diagnostic group was $-15.6 \pm$ SE 15.3, ($t = -1.02$, NS) while that for (female) sex was $31 \pm$ SE 17.5 ($t = 1.78$, $p = 0.08$). Age and cigarette smoking were not associated with contraction amplitude. Water swallow pharyngo-oesophageal wave velocity was also lower in patients (2.96 ± 0.56 cm/sec) than in controls (3.29 ± 0.87 cm/sec) a difference that was not significant on rank-sum testing but which was significant on multiple regression analysis ($t = -2.79$, $p < 0.01$). The discrepancy between the two statistical methods was due to the fact that females in the series (who comprised only two of the patient group but 10 of the control group) showed a significantly lower velocity than males. There was also a trend on regression analysis for the irradiated patients to have an increased duration of UOS relaxation, but only for bread swallows ($t = 1.9$, $p = < 0.07$). Continued cigarette smoking did not significantly influence the results.

The effect of the time interval (in months) following radiotherapy was assessed for all parameters by rank correlation. The two water swallow parameters which were shown to be reduced in the patient group also showed an inverse association with the post-treatment interval: for wet swallow after-contraction amplitude, $r_s = -0.42$ ($p < 0.05$), and for pharyngo-oesophageal wave velocity, $r_s = -0.47$ ($p < 0.03$). There was a similar reduction in bread swallow UOS after-contraction amplitudes ($r_s = -0.52$, $p < 0.02$). The remaining associations were all with temporal parameters. Increase in post-treatment interval was associated with an increase in the duration of pharyngeal contraction for water ($r_s = 0.53$, $p < 0.01$) and for bread swallows ($r_s = 0.47$, $p < 0.03$); an increase in duration of UOS relaxation for water ($r_s = 0.63$, $p < 0.002$) and for bread swallows ($r_s = 0.44$, $p < 0.05$): and an increase in duration of the upper oesophageal wave for water swallows ($r_s = 0.47$, $p < 0.03$). There was also a weak positive association with distal oesophageal peristaltic duration ($r_s = 0.34$, $0.1 > p > 0.05$).

The mean age of the nine patients with T_1 tumours was 69 years and the mean age of the remaining 10 patients was 63 years ($t = 1.75$, $p = < 0.1$). Although not significant, however, this difference is likely to account for the significantly lower mean maximum tonic pressure in the T_1 group (20 $\pm$ 9 mmHg) than in the group with more advanced tumours at presentation (33 $\pm$ 9 mmHg, $z = 2.45$, $p < 0.02$) whose pressures were almost identical to those of the control group (33 $\pm$ 14 mmHg).

7.1.3 Discussion

This is the first systematic study of the effects of cervical irradiation on pharyngo-oesophageal motility. Ekberg et al (1985) reported three patients with radiological evidence of chalasia (loss of stable tonus) following radiotherapy but one had also previously undergone a radical neck dissection and one had a bilateral vocal cord palsy. In the remaining male patients, studied 15 years following treatment, there was defective laryngeal elevation and abnormal laxity of the UOS. Ekberg (1987) later reported two further post-irradiation patients and concluded that radiotherapy produced reduced tone and defective peristalsis in the pharyngo-oesophageal segment. Both patients had also had thyroid surgery, however, and one had a tracheal stent in situ which is liable to have influenced the radiological findings, particularly as the dysmotility in this patient was confined to the lower part of the segment. McConnel et al (1988b) report one dysphagic patient investigated by manofluorometry after radiation, but the patient had also had a radical neck dissection and the primary tumour had been in the tongue base, which may have explained the findings of reduced tongue and laryngeal movement and of weakness of oropharyngeal propulsion. None of the patients in the present series had undergone any surgery except the performance of a laryngeal biopsy.

Clinical dysphagia following laryngeal irradiation is rare: only one patient in the present series complained of dysphagia, which was of mild degree. Poor voice quality, on the other hand, is a frequent finding, particularly in patients who continue to smoke and who show a greater derangement of acoustic indices on computerised vocal analysis (Lehman et al 1988). The motor abnormalities in the present study were, however, independent of cigarette smoking. There have been very few reports of the effect of radiotherapy on gastrointestinal motility. Thorpe et al (1982) report a case of an achalasia-like disturbance of oesophageal motility following extensive nasopharyngeal irradiation but the patient who had multiple cranial nerve palsies was, in effect, suffering from dysphagia of neurological origin. A similar patient is described in Section 7.3.

The principal effects of laryngeal irradiation in the present study were on temporal parameters, in particular on the water swallow pharyngo-oesophageal wave velocity. The reduction in velocity was more marked with an increasing post-treatment interval which was also associated with an increase in duration of pharyngeal and oesophageal contractions and of UOS relaxation, but not of UOS after-contraction. In normal subjects, the duration of UOS after-contraction shows a positive correlation with the other durations but not with contraction amplitude (Section 4.6). In the irradiated patients, therefore, there appears to have been an independent effect on UOS after-contraction amplitude, which was significantly lower than in the age-matched controls.

Tonic UOS pressure was lower in the total patient group by an insignificant amount. The only two other reports of radiation effects on gastrointestinal motility refer to chronic radiation injury of the anorectal segment (Varma et al 1985 and 1986), following a treatment regime similar to that of the present study. Results showed significant reductions in anal canal pressure and a diminution of the recto-sphincteric reflex. The external anal sphincter 'squeeze' pressure was relatively well--preserved. Rectal histology showed smooth muscle hypertrophy and a marked hypertrophy of the myenteric plexus with vacuolation of the nerve sheaths. Only the striated muscle segment of the upper gastrointestinal tract is exposed to significant radiation during laryngeal therapy and this may, like the external anal sphincter, be comparatively radio-resistant. The response in the associated autonomic myenteric plexus of the pharyngo-oesophageal segment may also be similar to that observed in the rectal autonomic fibres by Varma et al (1986). Histopathological studies of laryngectomy specimens, which include parts of the pharyngeal constrictors, are, therefore, presently under way to examine the validity of this hypothesis but at present there are no morphological data to explain the observed alterations in pharyngo-oesophageal motility. The finding of an associated trend towards increased peristaltic wave duration in the distal oesophagus, remote from the radiation field, tends, however, to support the presence of a radiation-induced alteration in neural control.

7.2 FUNCTIONAL CERVICAL DYSPHAGIA

Over an 18 month period, 30 patients with a principal complaint of cervical dysphagia but who had no neurological disease and no structural lesion in the cervical region to account for their symptom were referred for manometric investigation. Four patients were referred by gastroenterologists and the remainder by otolaryngologists. The aims of the study were to review the clinical features and to define the manometric patterns of these patients. Seven patients with radiological evidence of upper oesophageal webs or pharyngeal diverticula were also referred and their results are summarised here.

7.2.1 Methods

All patients underwent manometric investigation of the lower and upper oesophagus with the Gaeltec strain gauge assembly as described in Section 4.6.1. Eleven patients were studied before the introduction of routine bread swallow studies and only water swallow data were, therefore, available for analysis. The patients' clinical records were reviewed and an attempt was made to subdivide those with cervical dysphagia on the basis of any associated symptoms. The 30 patients comprised 20 males and 10 females aged 32 to 89 years (mean = 65 years). The results were compared with control data derived from a cohort of 27 age-matched healthy volunteers (described in Section 4.4 and Section 4.6) comprising 12 females and 15 males aged 28 to 77 years (mean = 61 years). Data analysis was by the Mann Whitney U-test. The findings were confirmed by multiple regression analysis of the results with age and sex because, although the mean ages of the patient and control groups were not significantly different on an unpaired t-test, there was a 12 year age difference between the oldest patient and the oldest control subject. Six of the patients also underwent prolonged ambulatory pH monitoring (see Section 5.1.1) but this investigation was felt to be inappropriate in the majority of the patients, many of whom were over 70 years of age.

The five patients with upper oesophageal webs comprised one male and four females aged 50 to 78 years (mean = 69 years) but one of the female patients had a history of local excision and radiotherapy of a floor of mouth carcinoma and so her results were considered separately from those of the other four patients. The two male patients studied with pharyngeal diverticula were aged 61 and 70 years.

7.2.2 **Results I: Clinical Features**

The principal associated symptoms in the 30 patients with cervical dysphagia but without a structural cervical abnormality are listed in Table 7.1. Males outnumbered females in all groups except in the group with associated globus sensation. Twelve patients experienced heartburn more than once per month. In seven patients cervical dysphagia was essentially an isolated symptom, although one patient also suffered from long-standing angina, and two had associated nausea and belching. pH monitoring results in the latter two patients were well within the normal range (total intraoesophageal acid exposure time = 1.1% and 2.9%). One patient complained also of slight hoarseness and had an epiphrenic diverticulum. Barium examination findings were normal in the remaining six patients, and one patient had had two such normal examinations. Four patients were studied following hospitalisation for an acute episode of upper oesophageal bolus obstruction. The two males (aged 45 and 49 years) had both experienced two such episodes. One had multiple small diverticula of the oesophageal body on barium meal examination, in association with frequent heartburn. The other attributed his symptoms to work-related stress and panic attacks during eating. The two females were aged 66 and 73 years. One gave a history of having had to eat slowly for many years following the diagnosis of a hiatus hernia.

Seven patients suffered from repeated choking episodes, present in three of these only during liquid swallows. Two of these had

TABLE 7.1 - Clinical Features of Patients with Cervical Dysphagia

PRINCIPAL ASSOCIATED SYMPTOM	n	MALE	FEMALE	AGE (years) MEDIAN (range)	HEARTBURN > monthly
Nil	7	6	1	66 (32 to 79)	-
Bolus obstruction	4	2	2	58 (45 to 72)	2
Choking	7	4	3	60 (38 to 88)	-
Heartburn	7	6	1	70 (55 to 89)	7
Globus	5	2	3	76 (59 to 82)	1
TOTAL	30	20	10	66 (32 to 89)	10

associated belching or suspected tertiary contractions on barium meal examination but pH monitoring results were normal (total AET = 0.3% and 3.4%). One of the males was mentally retarded and the oldest patient in this group (an 88 year old female) suffered from senile dementia. She also had tertiary contractions with free reflux on barium examination and her symptoms later responded to a conservative anti-reflux regime. A 53 year old female in this group gave a long history of severe panic attacks when she felt that a crumb had become lodged in her throat. The remaining male patient also choked repeatedly on solid foods, with occasional episodes of cough syncope.

There was only one female patient among the seven with associated regular heartburn, a 57 year old woman who had originally been seen with globus sensation and who had subsequently undergone removal of a parathyroid adenoma and was normocalcaemic. She developed postoperative cervical dysphagia and daily heartburn but her pH monitoring results were within the normal range (total AET = 7.1%). One of the younger male patients in this group also underwent pH monitoring, with similarly normal results (total AET = 2.9%). pH monitoring was not possible in a 62 year old male who had previously undergone a Nissen fundoplication and who had radiological evidence of poor epiglottic movement, as the pH probe appeared to catch on the epiglottis and could not be passed. The 89 year old male in this group was the oldest patient in the series and, like another elderly male, had to induce vomiting when solids became lodged in the pharynx. The two remaining patients were 75 year old males, one with a history of angina and the other who had a negative endoscopy and barium meal.

The five patients with associated globus sensation were all 59 to 82 years of age, in contrast to the mean age of 50 years in the 207 patients in whom globus sensation, rather than dysphagia, was the leading symptom (Figure 6.1, Page 226). The youngest patient also had complaints of heartburn and regurgitation, but pH monitoring results were normal (total AET = 7.0%). One patient had a history of hiatal repair and peptic ulcer surgery many years previously and the remaining patient's symptoms later responded to local therapy for a furred and hairy tongue.

Two of the female patients with uncomplicated webs had angular cheilitis and serum iron and ferritin levels at the lower limit of the normal ranges. One also had radiological evidence of a sliding hiatus hernia but both had pH monitoring results within the normal range (total AET = 1.5% and 3.2%). The remaining female patient complained of globus sensation in addition to dysphagia. She also developed angular cheilitis during the course of investigation, but her serum iron and ferritin levels were well within the laboratory reference range. In the only male patient with a web there were no associated signs or symptoms.

7.2.3 Results II: Manometric Investigation

An initial comparison was made of the manometric results in the 30 patients with cervical dysphagia and the findings in the 27 age-matched controls. No significant difference between the two groups was found in any of the 39 LOS, oesophageal body or UOS parameters tested on either the Mann-Whitney test or on multiple regression analysis with age and sex. As might be expected, in view of the wide age-range and of the heterogeneous nature of the associated clinical features in the patients studied, the manometric results were also very wide-ranging. For example, wet swallow UOS after-contraction ranged from 26 to 414 mmHg and bread swallow pharyngeal pressure from 5 to 221 mmHg. The patient results were, therefore, divided into four groups on the basis of their principal associated symptoms (Table 7.1). The patients with isolated cervical dysphagia or bolus obstruction were grouped together.

The results in each subgroup of patients were compared with those in the 27 control subjects using regression analysis with age and sex. In the patients with cervical dysphagia associated with either heartburn or the presence of a simple upper oesophageal web, no significant difference from the control group was demonstrated. The results obtained in the female patient with an oesophageal web following oral surgery and radiotherapy showed clear evidence of pharyngo-oesophageal incoordination during bread swallows; the minimum UOS relaxation pressure was -20 mmHg (control range = -17 to 21 mmHg) but the UOS pressure at the point of maximum pharyngeal contraction was 88 mmHg. During water swallows, however, the peak of the pharyngeal wave coincided with the minimum UOS pressure of 7 mmHg (control range = -3 to 8 mmHg).

The five patients with globus sensation showed a significant increase in peristaltic velocity (mean = 6.0 cm/sec) compared with controls (mean = 3.0 cm/sec, $t = 3.1$, $p = 0.005$). In the patients with isolated dysphagia or bolus obstruction, there was also a trend to increased peristaltic velocity ($t = 1.96$, $p = 0.06$) and a more significant increase in pharyngo-oesophageal wave velocity (mean = 4.2 cm/sec) compared with controls (mean = 3.2 cm/sec, $t = 2.26$, $p = 0.03$).

The greatest degree of manometric abnormality was present in the patients who experienced choking episodes. These patients had a significant increase in peristaltic amplitude (mean = 89 mmHg) compared with controls (mean = 54 mmHg, $t = 2.0$, $p < 0.05$), and an increase in the mean duration of pharyngeal contraction (1.80 sec) compared with the control subjects (mean = 1.26 sec, $t = 2.3$, $p = 0.03$). The mean maximum tonic UOS pressure in patients with choking was 25 mmHg compared with a mean value in the control group of 35 mmHg (NS). There was a corresponding reduction in the mean UOS pressure/length index in patients with choking (3.4 mmHg/cm) compared with controls (5.2 mmHg/cm, $t = -1.97$, $p = 0.07$). In the older of the two patients with pharyngeal diverticula, manometric examination was not possible as the catheter repeatedly became coiled within the pouch. In the other patient, all manometric results were within the normal range.

7.2.4 Discussion

The symptom of dysphagia can arise from a multitude of causes at the level of the pharynx, oesophagus or gastric fundus (Ott et al 1986). Over the past century there has clearly been a change in the relative importance assigned to the structural causes of dysphagia. StClair Thomson (1898) in a monograph on functional dysphagia, which he believed to be of psychogenic origin, advised that this diagnosis be considered only after the exclusion of carcinoma, aneurysm or oesophageal ulceration of traumatic, syphilitic or tuberculous origin. Otell and Coe (1935) also grouped globus hystericus and hysteria among 'rare' causes of dysphagia, ie among the aetiologies which were less common than pharyngeal diverticula or congenital oesophageal stenosis. It is obvious from the data presented in Chapter 6 that globus sensation is now a very common cause of cervical symptomatology in ENT practice. Also, 22% of the 207 patients described experienced some degree of dysphagia (Table 6.3, Page 218). In the present series, only patients whose globus sensation was of secondary importance to their cervical dysphagia were included in the study. This criterion resulted in a male:female ratio of 2:1, with a mean age of over 60 years, in the 30 patients without a structural cervical lesion. In those surveys of functional dysphagia where patients with a principal complaint of globus sensation have not been excluded, a majority of female patients has been observed (Vinson 1922, Elwood et al 1964). Ekberg and Wahlgren (1985) in their review of 854 dysphagic patients, found a female preponderance in subjects aged under 65 years, with a male preponderance in patients aged over 65 years.

The incidence of cervical dysphagia in female patients is also influenced by the reporting of upper oesophageal webs which have a 0 to 12% incidence in males and a 15 to 18% incidence in females (Elwood et al 1964, Ekberg and Wahlgren 1985). The one male patient with a web in the total group of 23 males referred for the investigation of cervical dysphagia in the present series represents an incidence of 4%, compared with a 29% incidence in the 14 dysphagic females studied. Three of the four women with webs had evidence of mucosal atrophy (angular cheilitis) and one had associated globus sensation. In the remaining patient the gross pharyngo-oesophageal incoordination during bread swallows suggested that her previous oral surgery and irradiation were much more important in the aetiology of her dysphagia than the presence of the web, as the manometric findings in the remaining four patients with webs were not significantly different from those in the control subjects. The functional significance of mucosal changes in the general population seems to remain as unclear as it was in the days of StClair Thomson (1898). He observed several instances of 'functional dysphagia' in 'cottagers' wives .... poor women leading a hard life, the hardness of it being increased by the necessity of expending money on milk, eggs and beef-tea' and also described the association of dysphagia and anaemia but added, 'whether as cause or effect I am unable to say'. Subsequent opinions remained divided on this point, with Vinson (1922) believing the anaemia to be secondary, and Paterson (1937) being of the opinion that microcytic hypochromic anaemia was a causal factor in the majority of women studied (who were mostly of reproductive age, ie aged 30 to 50 years). The epidemiological study of Welsh patients by Elwood et al (1964) found no evidence of a causal relationship between iron deficiency and dysphagia which was present in 1% of males and 5% of females. Also, only two of over 700 females under the age of 50 had oesophageal webs, whereas 14 webs were detected in older women. Bearing in mind the potential pit-falls of historical comparisons, it appears that women with webs, including the four in the present study, are now aged about 20 years older than those of 50 years ago. In a manner analogous to the changing demographic pattern of atrophic rhinitis, which was also a disease of females of reproductive age in the 1930s, the apparently changing age-association of oesophageal webs supports the presence of nutritional deficiency as an aetiological factor in some patients. Such deficiences are now more common in those of pensionable than of reproductive age. Webs are, however, known to arise in subjects without iron deficiency, not only in the general population where the condition may not be fully manifest (Elwood et al 1964) but also in the hospital setting, as in the present study. The aetiology of the angular cheilitis in the female patient with a web but with normal serum iron levels (and no evidence of oral candidiasis) remains unclear. It may be, therefore, that in some patients the aetiological factor is a dietary deficiency of a substance other than iron.

There are other factors which complicate the investigation of patients with cervical dysphagia. The first is the incidence of minor abnormalities of deglutition in the asymptomatic population which was found to be 17% in a radiological study of 150 patients without dysphagia (Ekberg and Nylander 1982a). Secondly, there is the 20% incidence of normal conventional radiological findings in dysphagic patients (Osborne et al 1960). Similar normal findings in their cineradiographic and manometric investigation of patients with oropharyngeal dysphagia led Hurwitz et al (1975) to suggest that 'oropharyngeal dysphagia exists in the general population without evidence of a specific causative disease'. The picture is further confused by the occurrence of psychogenic dysphagia (Lindsay 1955) and by the wide range of disorders which have in the past been loosely referred to as 'cricopharyngeal spasm' (Clerf and Putney 1942). This heterogeneity has been confirmed in the present series of 30 patients who were selected only by the presence of cervical dysphagia as the leading symptom in the absence of a local structural lesion. A review of the variety of associated symptoms suggested that the patients should be subdivided by clinical features and although this approach led to the creation of several groups each comprising only a small number of patients, the results to some extent validate this approach.

In patients with no associated symptoms, the only abnormality detected was an increase in pharyngo-oesophageal wave velocity, with a slight increase in peristaltic wave velocity, the latter being more marked in those with associated globus sensation. The results in patients with associated choking episodes were more clearly abnormal and showed a reduction in UOS pressure/length index on timed SPT, with an increase in the duration of pharyngeal contraction and an increase in peristaltic amplitude. While it is tempting to suggest that both the pharyngeal and peristaltic changes represented compensatory mechanisms to increase upper airway protection in the presence of UOS hypotonicity, only seven patients in this category have so far been studied and it remains to be seen whether these findings can be reproduced in a larger sample. With the exception of the female patient with an oesophageal web following treatment for oral carcinoma, no abnormality of bread swallowing was present in any group, but again this may be due to the fact that not all patients underwent bread swallow studies, although three of the seven patients with choking developed attacks only during liquid swallows. In these patients there may be defective protection of the laryngeal vestibule which has been demonstrated radiologically in 37% of patients with pharyngeal dysphagia (Ekberg and Wahlgren 1985) but is also present in asymptomatic subjects (Ekberg and Nylander 1982a). In patients with reflux, the incidence of cervical dysphagia was reported to be over 50% in a survey of 1000 patients (Henderson et al 1976), but only 15% also experienced choking attacks. Although the authors judged radiology and manometry (with a triple-lumen perfused catheter) to be 'disappointing' in the investigation of such patients, there was a tendency for reflux patients to exhibit premature closure of the cricopharyngeus. The importance of this observation was later questioned by the authors themselves as it bore no clear-cut relationship to the presence of cricopharyngeal symptoms (Henderson and Marryatt 1977). Both in the present study and in studies reported in Section 5.1 and Section 5.2, there was no association of reflux and UOS hypertonicity and none of the six patients with cervical dysphagia who underwent pH monitoring had an abnormal result. Gerhardt et al (1980a) also found no such association but in their group of 20 patients who had spontaneous choking episodes secondary to oesophagopharyngeal regurgitation, the amplitude of the oesophageal peristaltic wave was reduced, in contrast to the present series of patients with choking during eating or drinking, in whom mean peristaltic amplitude was increased.

Two patients in the present series had previously undergone surgical repair of hiatus hernia. It is known, however, that the cricopharyngeal dysphagia which is associated with GOR is not universally responsive to hiatal repair (Henderson and Marryatt 1977, Orringer 1980). The postoperative persistence of dysphagia has three possible causes. The first is that the surgery performed has not been an effective anti-reflux procedure, the second is that the original association of reflux and dysphagia was casual rather than causal and the third is that the procedure itself has induced dysphagia which is perceived in the cervical region. Cricopharyngeal myotomy has been advocated as an alternative treatment for reflux-associated cervical dysphagia, despite the potential hazard of an increase in oesophagopharyngeal reflux and regurgitation. In the present study, patients with choking episodes had a reduced UOS pressure/length index and no dysphagic patient had UOS hypertonicity. There was also a reduction in UOS tone in the patients identified as having reflux-associated laryngitis (Section 5.3.4). On the basis of these findings and those of Gerhardt et al (1980a) there is no evidence to suggest that cricopharyngeal myotomy is advantageous in cervical dysphagia and some indirect evidence that it may actually be deleterious. Pharyngeal weakness has also been cited as a cause of cervical dysphagia in elderly subjects (Kilman and Goyal 1976). The wide range of normal peristaltic amplitude in the 27 control subjects studied (14 to 146 mmHg) implies that this diagnosis is unlikely to be made purely on manometric grounds.

Many of the patients investigated in this study were extremely distressed by their symptoms which, in some cases, resulted in panic attacks or in social embarrassment and a reluctance to take meals in the company of other people. In the majority, including the only patient with a pharyngeal diverticulum, manometric findings were, therefore, surprisingly normal, particularly in view of the demonstrable abnormalities in patients who had undergone irradiation and yet were essentially symptom-free. Even in the small group studied, the patients who had choking episodes appeared to have a greater degree of manometric abnormality than patients with other symptoms and it is felt that this group should continue to be analysed separately in future studies. The study of swallows of solid boluses appears to be valuable in the detection of occasional gross abnormalities of pharyngo-oesophageal coordination and further justified by the finding of significant numbers of patients whose symptoms are present only while eating solid foods. Also, there is some evidence in the present study that the calculation of the UOS pressure/length index from a timed SPT may be a more sensitive discriminant than mean maximum tonic SPT pressure or RPT pressure. A nutritional survey of patients with upper oesophageal webs is planned, to establish whether or not a deficiency of nutrients other than iron is associated with mucosal changes. It can also be concluded that in future studies the magnitude of any reflux present should be assessed by pH monitoring in a greater number of patients where at all possible, and some form of psychometric evaluation should be included. Such additional assessments may allow a more precise classification of the functional causes of cervical dysphagia.

7.3 NEUROMUSCULAR DYSPHAGIA

Cervical dysphagia is known to be caused by a wide variety of neurological diseases (Edwards 1973) but there have been few manometric investigations of neurological dysphagia using modern techniques. The aims of this study were to determine whether there are any characteristic manometric abnormalities in patients with dysphagia of neurological origin, and to establish whether the presence of a vagal palsy caused any alteration in the patterns observed.

7.3.1 Methods

Fourteen patients with cervical dysphagia of neuromuscular origin were studied. A few had been referred to the ENT department with a vocal cord palsy and the remainder were referred from the department of neurology. The patients comprised nine males and five females, aged 20 to 84 years (mean = 62 years). Three patients had dysphagia following cerebrovascular accidents. Three patients had disease processes affecting the base of the skull - in one patient an advanced glomus jugulare tumour, in the second a recurrence of a squamous cell tumour of the oropharynx and in the third osteoradionecrosis following radiotherapy to a nasopharyngeal sarcoma 30 years previously. This last patient had for years been unable to swallow adequately and was managed at home with an indwelling nasogastric tube. The two youngest patients studied were a 20 year old male with the oculopharyngeal syndrome and a 42 year old female who had developed dysphagia following encephalitis. Four further patients had dysphagia in association with motor neurone disease (2 patients), multiple sclerosis or herniation of the cerebellar tonsils.

The neurological signs in the two remaining patients were of obscure aetiology. One had an extensive left brachial plexus palsy and a left vocal cord palsy, but with no evidence of an apical pulmonary lesion, and the other was an 84 year old women with a short history of hoarseness and dysphagia in association with a left vocal cord palsy. It was not clear whether this was an uncomplicated idiopathic recurrent laryngeal nerve palsy or whether she had a focal central lesion of vascular origin. Vocal cord palsies were also present in all three of the patients with base of skull erosion and in one of the cerebrovascular accident patients. Of the six vocal cord palsy patients, therefore, four had a high vagal lesion and in two the site of the lesion was undetermined. Four were left-sided and two were right-sided.

All patients underwent the modified manometric protocol used in the older healthy volunteers (Section 4.6.1). The results were compared with those in a cohort of 24 of the healthy volunteers whose results are described in Chapter 4. The control group comprised 14 males and 10 females aged 20 to 77 years (mean = 63 years, ie not significantly different from the patient group on an unpaired t-test). The six patients with vocal cord palsies were aged 62 to 84 years (median = 69 years) and their results were also compared separately with those in 15 of the control subjects aged 62 to 77 years (median = 68 years, NS). The data were analysed by the Mann-Whitney U-test.

7.3.2 Results

There were no significant differences in any LOS or oesophageal peristalsis parameter between patients and controls. Median maximum tonic UOS pressure in the control group (35 mmHg) was somewhat higher than in the patient group (21 mmHg) although the difference was not significant at the present sample size ($z = -1.62$, $p = 0.11$). The distribution of peristaltic amplitudes and of tonic UOS pressures are illustrated in Figure 7.1. Studies of pharyngo-oesophageal motility during water and bread swallows revealed significant differences in UOS after-contraction between the two groups. During water swallows, the median UOS after-contraction in controls was 89 mmHg, while that in the patients was 56 mmHg ($z = -2.48$, $p < 0.02$).

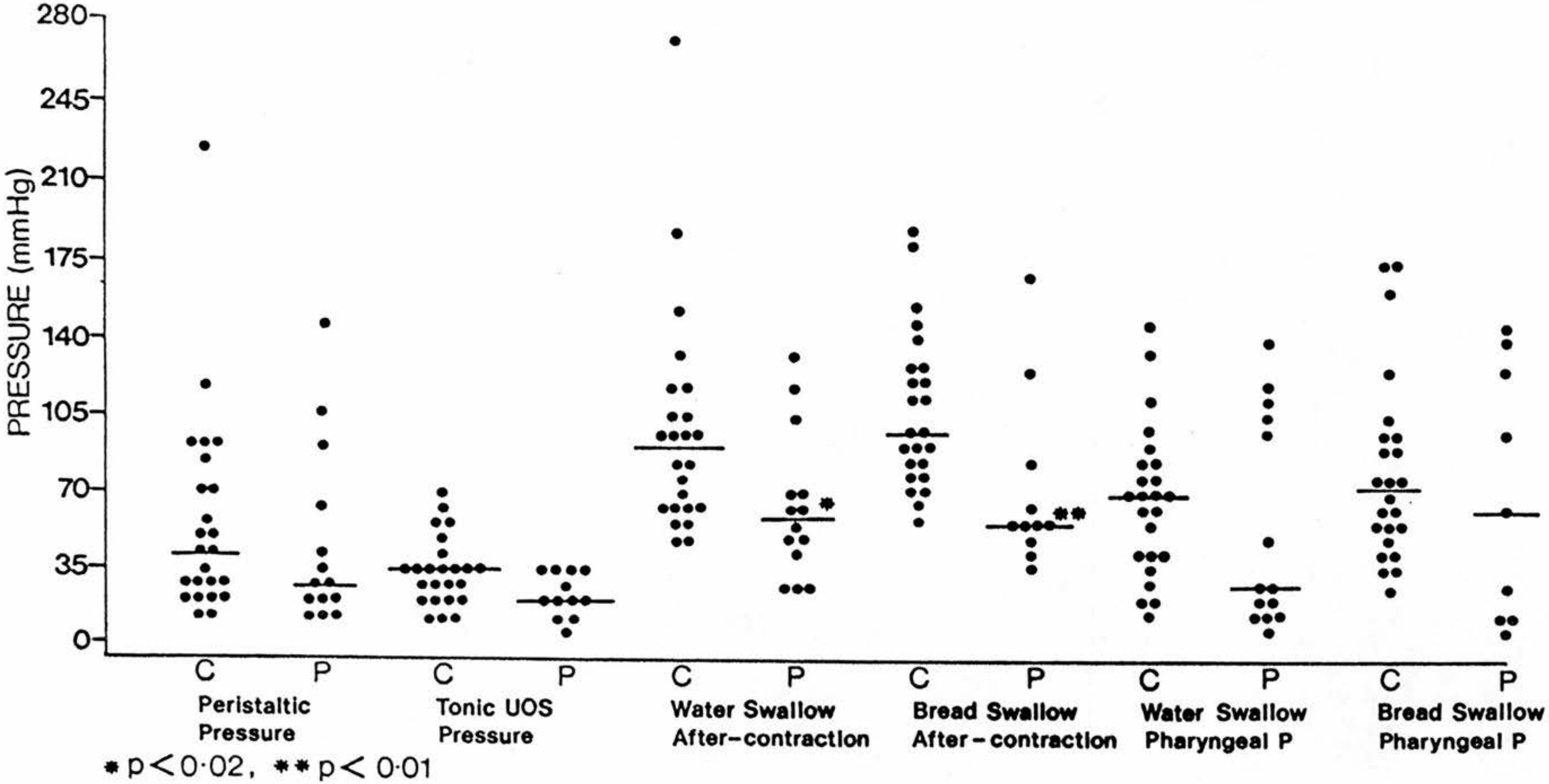


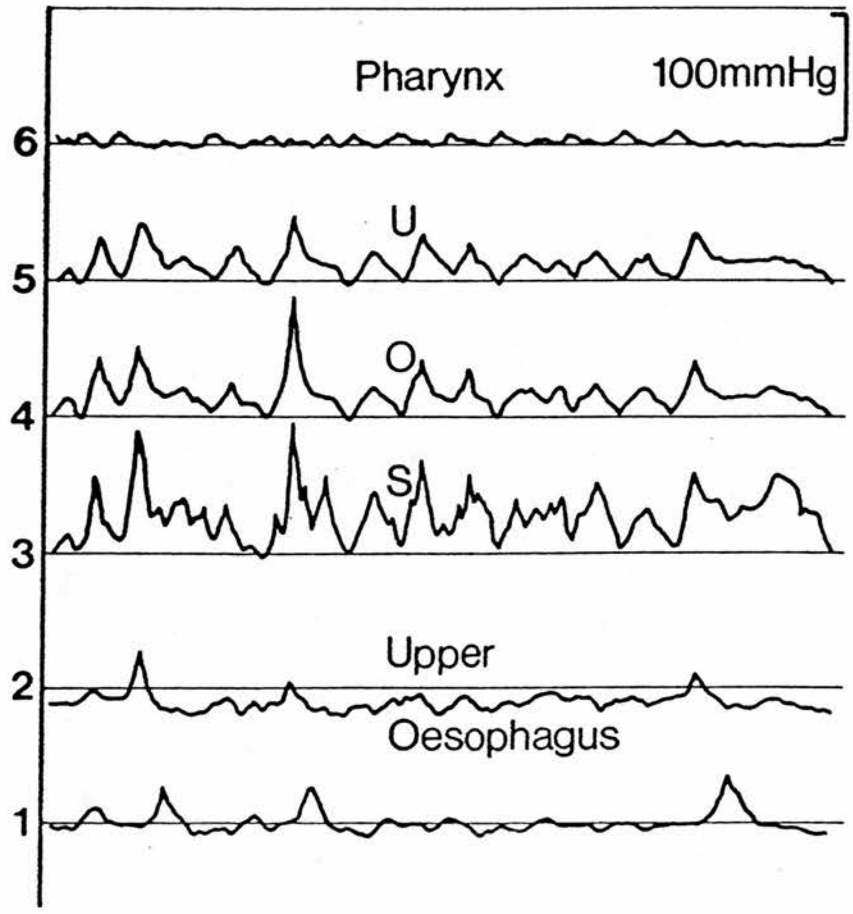
FIGURE 7.1 - Manometric Results in 24 Volunteers and 14 Patients with Neurological Dysphagia

(medians are indicated)

Bread swallow data were not available in three of the patients. The patient who was usually fed by nasogastric tube was unable to swallow solid food and in the post-encephalitic patient a double bread swallow pattern was consistently present. In the patient with an idiopathic paralysis of the left brachial plexus and vocal cord, a bizarre multiple swallow pattern was observed during his repeated attempts to pass the bread bolus through the pharyngo-oesophageal segment (Figure 7.2). This patient was also seen to aspirate barium during radiological evaluation of swallowing. The young male patient with the oculopharyngeal syndrome exhibited excessive sphincter-on-catheter movement during bread swallows, so that the UOS tracing appeared in the sensor which was sited 3 cm above the zone of maximum tonic UOS pressure at rest. The minimum recorded in the three sensors sited within the UOS at rest was correspondingly low (-15 mmHg).

In the remaining 11 patients, median bread swallow UOS after-contraction pressure (54 mmHg) was almost 40 mmHg lower than that in controls (93 mmHg, $z = -2.95$, $p < 0.01$, Figure 7.1). UOS minimum relaxation pressure during water swallows was also significantly higher in controls (median = 4.6 mmHg) than in patients (median = -1.0 mmHg, $z = -2.75$, $p < 0.01$). The UOS residual pressure at the time of peak pharyngeal contraction was also significantly greater in controls (median = 10.4 mmHg) than in patients (median = 4.4 mmHg, $z = -2.34$, $p < 0.02$). During bread swallows, however, the median minimum UOS relaxation pressure was similar in controls (1.2 mmHg) and patients (3.4 mmHg, NS), as was the UOS pressure at the peak of the pharyngeal pressure wave (12.0 mmHg in controls and 8.8 mmHg in patients, NS). Pharyngeal contraction amplitude was slightly greater in the control group (Figure 7.1) but the difference was significant for neither water nor bread swallows. The patient with oculopharyngeal muscular dystrophy had a mean water swallow pharyngeal pressure of 24 mmHg. The duration and velocity of events in the pharynx, UOS or upper oesophagus were also not significantly different between the two groups.

FIGURE 7.2 - A 12-Event Bread Swallow Sequence in a Patient with Idiopathic Neurological Dysphagia



The separate analysis of the results from the six patients in whom a vocal cord palsy was present with those of the 15 age-matched controls showed similar significant reductions in UOS water swallow after-contraction and relaxation pressures between the two groups. The reduction in bread swallow UOS after-contraction was also significant ($z = -2.66$, $p < 0.01$). An additional abnormality in the patients with vagal palsy was a significant reduction in pharyngeal contraction amplitude. During water swallows, the median pharyngeal pressure in patients was 35 mmHg compared with a median value of 70 mmHg in the 15 controls $z = -2.02$, $p < 0.05$). For bread swallows, median pharyngeal pressure in patients was 30 mmHg while the median control value was 90 mmHg ($z = -2.6$, $p < 0.01$). In one patient both pressures were only 7 mmHg. Mean maximum tonic UOS pressure was not significantly different between the two groups but there was a trend in the patient group to lower mean UOS pressure ($z = -1.87$, $p = 0.06$) and to a reduction in the pressure/length index ($z = -1.72$, $p = 0.09$). One of the patients, who had severe dysphagia following a cerebrovascular accident with vagal involvement, had marked incoordination of the pharyngeal wave with UOS relaxation during bread swallows.

When the results in the eight patients without a vocal cord palsy were analysed separately, the only significant difference from the results in age-matched controls was the reduction in UOS wet swallow minimum relaxation pressure ($z = -2.05$, $p < 0.05$).

7.3.3 Discussion

The present study constitutes a preliminary report on the use of upper oesophageal manometry in the evaluation of neurological dysphagia. Despite the heterogeneity of the 14 patients studied, several significant differences from the age-matched controls have been demonstrated. The importance of concomitant vagal palsy as a determinant of pharyngo-oesophageal motility is also apparent. The cineradiographic studies of Lund and Ardran (1964), showed no abnormality of cricopharyngeal function in a large number of patients with unilateral or bilateral recurrent laryngeal nerve palsies. It was concluded that the human UOS was likely to be supplied by the pharyngeal branch of the vagus via the pharyngeal plexus. In four of the present series of six patients with a vocal cord palsy a lesion above the origin of this branch (base of skull in three, central in one patient) was identified. A central vascular lesion was also thought to be very likely in one further patient (an 84 year old woman). The aetiology of the brachial plexus and vocal cord palsy in the remaining 62 year old male remains obscure despite extensive neurological investigation. The abnormalities demonstrated in this group were a significant reduction in pharyngeal and UOS after-contraction pressures and in UOS minimum relaxation pressure. These differences are likely to account for much of the abnormality observed in the total group of 14 patients with neurological dysphagia, as separate analysis of the eight patients with normal vocal cord function revealed a significant reduction only in water swallow minimum UOS relaxation pressure. In this small series of patients with a unilateral vagal palsy there was also a trend towards a reduction in mean tonic pressure and in pressure/length index of the UOS, but as there was no reduction in maximum tonic UOS pressure. The principal effect of vagal paralysis in the patients studied may, therefore, have been on the muscles adjacent to the cricopharyngeus which contribute to the high pressure zone. Such a selectivity, if present, may be related to the extent of vagal involvement by disease and to the diameter of the affected neurones (Lund and Palmer 1969). Further studies are planned to confirm these findings in a larger group of patients with high vagal palsy, and to confirm the radiological findings of Lund and Ardran (1964) that a paralysis known to be confined to the recurrent laryngeal branches of the vagus does not significantly influence manometric results. A 45% incidence of dysphagia following acute cerebrovascular accident has been recently reported and it appears that some patients are more susceptible to disturbance of function in one hemisphere. Although swallowing pathways are represented bilaterally, the other hemisphere takes some time to compensate, but the reasons for this are unclear (Gordon et al 1987). It is hoped to define the manometric pattern of transient dysphagia following unilateral hemispheric lesions in a future study.

The importance of reduced pharyngeal peristalsis in dysphagia secondary to bulbar palsy was identified in the early days of upper oesophageal manometry in a study of four patients with bulbar poliomyelitis (Kramer et al 1957). In the present study pharyngeal pressures were significantly reduced during both water and bread swallows in patients with a vagal palsy. On rare occasions, complete pharyngeal palsy is reported to be associated with failure of UOS opening (Lund 1968, Orringer 1980). No patient in the present series had UOS achalasia, reflecting the uniformly unilateral nature of the vagal involvement. The patient with oculopharyngeal muscular dystrophy had a pharyngeal pressure within the normal range, although in older patients with this rare syndrome, a significant reduction in pharyngeal amplitude has been observed (Fradet et al 1988). In the patient who had a vagal palsy following osteoradionecrosis of the skull base, mean maximum tonic UOS pressure was ony 6 mmHg (control range = 11 to 67 mmHg). Thorpe et al (1982) reported a similar instance of UOS hypotension following cervical radiation neuropathy, with associated oesophageal aperistalsis and LOS achalasia. The patient in the present study had low amplitude but peristaltic contractions in the oesophageal body, and LOS relaxation appeared to be within normal limits. Abnormality of oesophageal peristalsis was, however, noted in the patient who exhibited multiple UOS pressure complexes during bread swallows. These pressure changes were only intermittently associated with a contraction wave in the cervical oesophagus (Figure 7.2). Ask and Tibbling (1980) also observed that continuous swallowing produced a consistent response only in the UOS and not in the tubular oesophagus and Ekberg et al (1985) described absent or delayed upper oesophageal peristalsis in the presence of normal UOS deglutition responses in a radiological study of four patients with chalasia of the UOS.

Attempts have also been made to identify the characteristic radiological appearances of different types of neuromuscular disorder (Silbiger et al 1967) but the small numbers of patients in each group precluded any such diagnostic classification in the present series. One important factor in neuromuscular dysphagia which can be assessed radiologically, but not manometrically, is the presence of laryngeal aspiration (McIntosh et al 1987). Aspiration may be due to a delay in the initiation of the swallow reflex which is the commonest radiological abnormality in a study of 38 patients studied following cerebrovascular accidents (Veis and Logemann 1985), or to failure of UOS relaxation (Schultz et al 1979). The mechanisms for the maintenance of laryngeal competence were investigated recently by Shin et al (1988) in a series of human and feline experiments. The protective increase in subglottic pressure during laryngeal descent was found to be preserved even after section of one recurrent laryngeal nerve, but it was concluded that preservation of the sensory function of the superior laryngeal nerve was probably necessary for full airway protection.

The present results support the continued use of both water and bread swallows in patients with cervical dysphagia. Three patients who had normal coordination of water swallow motility had grossly abnormal bread swallow patterns. The comparison of the minimum UOS relaxation pressure with the UOS pressure at the peak of the pharyngeal contraction is also useful. Where the minimum UOS pressure has a markedly negative value, an excessive degree of artifactual catheter movement can be inferred, but the true extent of UOS opening cannot be assesed. The UOS residual pressure at peak pharyngeal pressure is not only a more accurate determinant of the UOS relaxation but also demonstrates the presence of gross pharyngo-oesophageal incoordination. Two groups of patients have now been identified in whom the UOS pressure/length index appears to be a more sensitive indicator of abnormality than the mean maximum tonic UOS pressure - the vagal palsy patients reported here and the patients with repeated choking episodes described in Section 7.2. Although this finding requires to be validated in a larger group of similar patients, it is possible that in certain disease states, some of the abnormality of the upper high pressure zone is located outwith the cricopharyngeus proper, in the adjacent contributory muscles. It is, therefore, planned to retain the pressure/length index of UOS tone in future studies. Many of the neuromuscular conditions which may affect pharyngo-oesophageal motility are either rarely encountered or are associated with dysphagia only occasionally and at varying stages of the disease process. While the long-term aims of manometric investigation are to establish both disease- and site-specific motility patterns, a reasonable interim approach may be the separate analysis of the results of individual patients, particularly with a view to assessing any possible benefits of cricopharyngeal myotomy which may be indicated in the presence of severe pharyngeal palsy, UOS achalasia or pharyngo-oesophageal incoordination.

8. GENERAL DISCUSSION

'What we call the beginning is often the end
And to make an end is to make a beginning.
The end is where we start from'. T S Eliot 1944

This thesis presents an investigation into pharyngo-oesophageal motility in health and disease. The initial aim of the study was to apply recent advances in electronic technology to the development of a reliable manometric method for the evaluation of UOS function. The inherent problems of UOS manometry - the presence of radial and axial asymmetry, the rapid sequence of events on deglutition and the sensitivity of the area to water from infused catheter systems - have been recognised for over 10 years. It is also known that the optimum sensor for the registration of pharyngeal contractions and, therefore, of pharyngo-oesophageal coordination is the intraluminal strain gauge. Although this type of transducer was developed almost 40 years ago (Gauer and Gienapp 1950), very few workers had previously used strain gauges to study pharyngeal motility and most manufacturers mounted catheters with only a single annular transducer or a series of three radially-disposed strain gauges (Weihrauch et al 1980b, Rex et al 1988). The former allows for UOS radial asymmetry but does not allow simultaneous registration of pharyngeal pressure while the latter does not provide adequate circumferential pressure sampling. The majority of clinical laboratories are, as yet, primarily concerned with motility studies of the LOS and oesophageal body for which a low-compliance capillary infusion pump (Arndorfer et al 1977) and a perfused catheter have a satisfactory rate of pressure rise and of frequency response. Also, the cost of a single strain gauge transducer approaches that of a conventional catheter. As many laboratories have already acquired a great deal of experience and a large databank of normal values with polyvinyl catheters, it is perhaps not surprising that the vast majority of manometric studies world-wide continue to be performed with equipment of the Arndorfer type.

The paucity of reports of the use of solid-state, digitised recording systems (Fradet et al 1988) is more remarkable in view of the increasingly widespread use of digitised oesophageal pH recording, and the introduction by at least three major centres in North America and Europe of the on-line computer analysis of analogue recordings (De Vault et al 1987, McConnel et al 1988a, De Bondt et al 1988).

The early studies described here (Pages 87 to 116) report on the use of a six-sensor strain gauge assembly with a computerised waveform analysis system (GR800, Gaeltec Research Ltd). At the outset, this combination was felt to offer several advantages over conventional methods in the study of both lower and upper oesophageal motility. The strain gauge assembly is one of the first to incorporate multiple catheter-mounted transducers, and was designed with a three-sensor level which could be positioned within the UOS during studies of pharyngo-oesophageal motility. Its narrow diameter (2.8 mm) and non-perfused structure made it seem likely that the magnitude of observed pressures would be more physiological and less indicative of a tension response to muscle stretch (Lydon et al 1975). The frequency response of the transducers (several thousand Hz) was known to be well in excess of the requirement for accurate pharyngeal recording (Orlowski et al 1982). The theoretical advantages of the computer recorder were its high rate of pressure-sampling (32/sec), its temporal resolution (0.01 sec), the ease of adjustment of baseline pressure to intragastric or intrapharyngeal zero reference, the automatic timing of peak-to-peak intervals and the generation of a digital printout which was likely to reduce observer error. For UOS deglutition studies the ability to expand segments of the graphic display allowed accurate marking of pressure and temporal events. The complete GR800 system is mounted on a single trolley and is more readily stored and transported than an infusion pump and chart recorder which occupy greater laboratory space.

Before the insertion of an analogue output module into the GR800 mother board, a preliminary assessment of the computer was made by using it to perform a repeat study with an identical protocol following conventional manometric evaluation of lower and upper oesophageal motility in 39 patients with cervical symptoms. The study was subject to constraints in design in order not to compromise patient management and the results indicate a variation of around 30 to 40% between the two methods (Table 4.1, Page 93). Most of this difference was attributable to biological variation and to variation in radial pressure sampling by the Arndorfer catheter. Several useful observations were made, including the value of repeatability coefficients, which have also been used recently by McConnel et al (1988a) to give an estimate of relative variance of different manometric parameters. It was also felt that tonic LOS pressure measurements during SPT would be rendered less variable by calculating the average of the maximum tonic pressure zones in each channel as opposed to the mean tonic pressure over the whole LOS length. Certain parameters of greater than average variation were identified - notably UOS minimum relaxation pressure and UOS swallow complex duration.

The problems of intrasubject variation and catheter rotation were overcome in the ensuing study by the simultaneous recording of the output signal of four of the six strain gauges on the GR800 and Elcomatic 750 recorders. The instantaneous analogue conversion of the signal also made it possible to compare directly the performance of the two recorders by the application of a known pressure of 50 mmHg from a sphygmomanometer. Both recording systems showed a maximum bias of under 10% during this bench test. Both sets of recorded pressures were a few mmHg greater than the applied pressure but the limits of agreement were 2.3 mmHg wider with the chart recorder than with the GR800, ie the latter showed a slightly superior recording fidelity. The in vivo comparison of the two recorders in 21 subjects indicated a variation of 5 to 10% between the two methods for pressures in the LOS and oesophageal body. The variation was 2 to 10% for UOS RPT pressure and 3 to 9% for UOS SPT pressure (Table 4.2, Page 102). The greater variation of peristaltic wave duration was attributed to a greater degree of observer error. In addition to the greater recording fidelity, the GR800 recorder also provided a direct digital output relative to intragastric or intrapharyngeal zero reference and an accurate calculation of tonic sphinter pressures. The inability to derive accurate mean pressures from a series of asymmetrical respiratory fluctuations in vivo is likely to be a more potent souce of error during the manual analysis of chart recordings than any minor reduction in pressure recording fidelity. The GR800 computerised waveform analysis system thus appears to be superior to a conventional analogue recorder in several respects. The system is also less expensive than comparable chart recorders and takes up minimal laboratory space. The GR800 requires less operational and maintenance expertise than a capillary infusion system, a feature likely to appeal to prospective investigators without previous manometric experience. Gaeltec Research Ltd are also currently developing a fully automated analysis programme for the LOS and oesophageal body, of the type currently used with an online computer to analyse analogue-recorded data. The primary use of a solid-state recorder greatly simplifies the performance of automated analysis and obviates the need for an additional computer.

The performance of the Gaeltec strain gauge assembly was then compared with that of a 4.7 mm diameter multilumen perfused catheter in a study of 23 patients with cervical symptoms. Both LOS and UOS maximum tonic pressure were greater when recorded by the perfused catheter, as was mean distal oesophageal peristaltic amplitude, but the difference was significant only for tonic UOS pressure (Table 4.3, Page 111). Making an allowance for estimated intrasubject variation, it seems that tonic UOS pressure was more susceptible than LOS or peristaltic pressure to the methodological variables of catheter diameter and sensor orientation. The Gaeltec catheter tonic UOS pressures were around 35% lower than the Arndorfer catheter pressures. The marked length/ tension response of the UOS has also been shown by the recording of higher pressures with a round catheter as opposed to an oval catheter which conforms to the slit-like configuration of the UOS (Green et al 1986, Kahrilas et al 1987a). It was felt that the pressures derived from the fine-bore, non-irritant Gaeltec assembly of sensitive strain gauges were more likely to reflect true physiological UOS tone. In the LOS, the Gaeltec catheter recorded pressures were only 8 to 10% lower than those of the Arndorfer catheter. The anticipated superior performance of the strain gauges in the registraton of rapid pharyngeal transients was also confirmed by the significantly greater pharyngeal pressure recorded with the Gaeltec catheter. Two principal conclusions can be drawn from this study. Firstly, in the lower oesophagus the use of a low-compliance infusion system produces results which do not greatly differ from those of a strain gauge assembly, despite considerable differences in cicumferential sampling. Secondly, the UOS is much more susceptible to the characteristics of the recording catheter, ie the Heisenberg uncertainty principle is even more applicable to the study of UOS motility than to the investigation of the lower oesophagus (Kaye and Showalter 1974).

Having validated the strain gauge assembly and the GR800 recorder as an accurate system for manometric study, a group of 67 volunteers was investigated. This constitutes the largest detailed study of normal pharyngo-oesophageal motility to date, and also establishes normal ranges for the use of fine-bore strain gauge assemblies in the lower oesophagus. The investigation has contributed to the understanding of UOS physiology and of the age and sex variables in normal UOS motility, and addresses some new aspects of the methodological problems of pharyngo-oesophageal manometry. The study also incorporates the first comparison of the performance of strain gauge transducers with that of a modified sleeve device in the recording of UOS tonic pressure. This is also an important contribution. The principal studies of UOS function in recent years have been performed in North America.

For prolonged studies of UOS motility during sleep (Kahrilas et al 1987b), acid perfusion (Anvari et al 1988, Vakil et al 1988) or acute stress (Cook et al 1987) the sleeve device has been used. For studies of pharyngo-oesophageal motility during swallows of different volume (Cook et al 1988a) or consistency (Castell et al 1988), one or two intraluminal strain gauges have been used. There has also been a recent increase in manofluorometric investigation with either strain gauges (McConnel 1988, Cerenko et al 1989) or with a sleeve device in the UOS used in conjunction with a pair of pharyngeal strain gauges mounted on a separate catheter (Kahrilas et al 1988a). When the Dent sleeve was first modified for use in the UOS, its performance was compared with that of perfused catheters (Kahrilas et al 1987a) but not with strain gauges. The present results in 50 healthy volunteers indicate significantly different findings for both tonic and peak UOS pressures measured by the sleeve sensor, the sleeve catheter side-holes and the strain gauge assembly (Table 4.5, Page 125). Although sleeve sensor pressures were greater than the average of the four side-holes, the comparison of the sleeve sensor with individual side-holes (Table 4.6a, Page 128) indicated that the greatest mean pressure was recorded by the anterior side-hole. The maximum pressure with the strain gauge assembly, as in previous reports (Hellemans et al 1981), were in the posterior plane (Figure 4.7, Page 129) suggesting that the sleeve diaphragm, which was orientated posteriorly in the UOS, is somewhat less pressure-sensitive than an open, perfused capillary tube. Also, although it has been claimed that one of the great advantages of the sleeve sensor is its rapid rate of pressure fall (200 mmHg/0.1 sec), the results of wet swallow analysis indicated that a shorter time to minimum relaxation pressure was recorded in the adjacent side-hole (Table 4.7, Page 134).

The sleeve catheter was not of course initially developed for this type of UOS motility study. Dent (1976) designed the sleeve catheter to track LOS relaxation during peristaltic studies. Recent evidence suggests, however, that only the proximal part of the diaphragm adjacent to the perfusion port can accurately reproduce LOS relaxations (Wallin et al 1988). A similar finding in the UOS required that the sleeve be sited with its proximal end in the sphincter during prolonged acid exposure studies (Section 5.2) in order to produce a stable baseline pressure. In any case, the accurate recording of UOS relaxation is of limited value in the absence of both accurate UOS after-contraction and pharyngeal pressure measurements. Although the use of a sleeve device together with a separate pharyngeal strain gauge assembly and an oral suction catheter to reduce the frequency of dry swallowing is feasible in a study of eight healthy subjects (Kahrilas et al 1988a) it is a very cumbersome and uncomfortable approach for routine clinical use. In the LOS, the limited radial sampling of the D-shaped sleeve sensor is of less consequence than in the UOS whose greater radial asymmetry results in very different tonic pressure measurements with even minor differences in orientation (Figure 4.6, Page 127). In summary, the sleeve catheter offers no practical advantage over a fine-bore assembly of radially-sensitive strain gauges, except during prolonged UOS pressure monitoring. Before the limitations of the sleeve catheter had been identified, 31 globus patients had been studied with the device. The results are included (Table 6.10, Page 246) because the trends observed were similar to those with the two other catheters used and thus support the conclusions on pharyngo-oesophageal dysmotility in globus sensation.

The description of LOS radial asymmetry in 50 healthy volunteers appears to constitute one of the largest series reported. Winans (1977) made his original observations in 10 subjects and Welch and Drake (1980) based their conclusions on the findings in 18 subjects. Table 4.4b (Page 122) and Figure 4.4 (Page 123) confirm the lower pressures present in the right and anterior segments of the LOS. For routine clinical manometry many centres continue to use triple-lumen tubes whose side-holes may be distributed over only 180^{o}. This may lead to considerable measurement error due to catheter rotation and to a disappointing 43% variability in tonic LOS pressure measurement (Chattopadhyay and Pope 1979). The present study also shows that LOS RPT pressures are more variable and less repeatable than tonic SPT pressure (Table 4.3, Page 111; Table 4.4a, Page 122; Table 4.8, Page 136), a finding attributed to intrasubject variability in breath-holding. The measurement error of tonic SPT pressures is largely due to inter-observer variation which is reduced by the computation of accurate mid-respiratory pressure by the GR800 with an associated variability on repeat testing of only 27%. The fall in peristaltic pressure, the only parameter to show a significant difference on repeat testing (Table 4.8, Page 136) may be due to a lesser degree of anxiety during the second examination as stress induces an increase in peristaltic amplitude (Young et al 1987, Anderson et al 1989). This is also an important observation as peristaltic amplitude is one of the most commonly-used parameters of clinical manometry. The wide normal range of peristaltic amplitude is likewise clinically relevant. Using an X + 2 SD definition, Richter et al (1987) calculated the upper limit of the normal range to be 180 mmHg. The comparable figure in the present study was 167 mmHg. The increase in peristaltic amplitude in normal females was not significant, although the regression analysis of a large group of patients and volunteers revealed that peristaltic amplitude in females was significantly greater than in males. Richter et al (1987) found a peak in peristaltic amplitude in the fifth decade but in the present study there was a more steady decline with increasing age so that volunteers aged 59 years or over had a mean amplitude 40 mmHg less than that in the younger volunteers (Table 4.10, Page 177). The inter-relationships of peristaltic velocity and duration with contraction amplitude are less clear. No significant association of these three parameters was established in 72 volunteers and patients. This may be due to the measurement error in the calculation of peristaltic duration and to the independence of age of peristaltic velocity (Hollis and Castell 1974).

The weak positive association of normal tonic pressures in the lower and upper oesophageal sphincters is also of considerable interest. Firstly, it supports the later finding that chronic oesophageal acid exposure does not increase UOS tone (Section 5.2). Secondly, it suggests some support for the hypothesis that a generalised 'increase in visceromotor tone' can influence both sphincters (Malcomson 1968). It has also been suggested that a diffuse neuromuscular derangement can give rise to oesophageal contraction abnormalities with concomitant large bowel disease (Clouse and Eckert 1986), although the association may be due to a common underlying psychological disturbance (Richter et al 1986b). It is also possible that the association of LOS and UOS tonic pressures in the present study is a chance finding. Certainly, if there is some general neuromuscular 'setting' of upper gastro-intestinal motility, it does not apply to peristaltic amplitude, which showed no association with LOS pressure or, on regression analysis for age, with UOS pressure.

In view of the long-standing debate about the optimum measurement of tonic LOS pressure, it is not surprising that at the outset of this study even less was known of the optimum parameters of UOS tonic pressure measurement, about which several conclusions can be drawn from the present results in healthy volunteers. The use of a circumferential strain gauge is reported to give accurate UOS tonic pressure measurements (Weihrauch 1980b, Castell et al 1988, Rex et al 1988). An annular sensor yields a pressure value which samples the entire circumference of the sphincter and which is, therefore, independent of catheter orientation. While this uniform sampling appears to increase the repeatability of UOS tonic pressure recordings, a catheter with multiple radially-sensitive transducers not only gives repeatable results (CR = 0.21, Table 4.8, Page 136) but also gives important information on radial and axial asymmetry which is not available with an annular transducer. The marked increase in anteroposterior UOS pressure has been confirmed in this study (Figure 4.7, Page 129). The presence of more distal maximum tonic pressure in the posterior plane (Welch et al 1979) was also confirmed, but the sphincter was found to show much less asymmetry in females. The posterior deficiency of the longitudinal fibres of the upper oesophagus in Laimer's triangle (Zaino et al 1967, Parrish 1968) may result in the absence posteriorly of a high pressure zone below the level of the cricopharyngeus. A posteriorly orientated sensor thus registers near-maximum UOS pressure on entering the sphincter during SPT (Figure 4.9, Page 131) whereas anteriorly the major extra-cricopharyngeal component of the high pressure zone may be the anterior attachment of the longitudinal muscle bands below the cricopharyngeus (Birmingham 1899). In females, the smaller laryngeal cartilages may contribute to the presence of less well-defined muscle bands and, perhaps, to a lesser deficiency in Laimer's triangle. It can also be postulated that the greater axial uniformity of pressures in the posterior plane in normal females implies a less well-defined 'dehiscence' of Killian, also because of a lesser degree of anterior pull on the inferior constrictor fibres by the smaller laryngeal framework. This hypothesis, which would explain the sex difference in pharyngeal pulsion diverticulum formation, merits further study by anatomical dissection.

The single sensor maximum tonic pressure was not found to be a useful additional discriminant to mean maximum tonic pressure, probably because of the close correlation of those two variables (r_s = 0.90, Table 4.11, Page 180). The maximum zones of UOS pressure are also in part created by the anterior mass of the larynx (Welch et al 1979) and this accounts for some of the persistence of an upper high pressure zone following cricopharyngeal myotomy. The present study provides some evidence that the performance of a timed SPT with 20 sec at each 0.5 cm station may provide more sensitive indices of UOS tone than maximum tonic pressure. In small samples of patients with choking episodes or vagal palsy, a reduction in the derived pressure/length index of the sphincter has been observed where the corresponding fall in maximum tonic pressure was unremarkable. The study also shows that the performance of a UOS RPT during quiet respiration with a fine-bore catheter yields pressures which are closely correlated with SPT pressures and of a similar magnitude to maximum tonic pressures (Figure 4.16, Page 182). In the LOS, RPT pressures with the same catheter were significantly greater than maximum tonic SPT pressure (Figure 4.4, Page 123), yet the LOS is less sensitive to catheter variables than the UOS. The superior agreement of RPT and SPT pressures in the UOS is probably due to the performance of UOS RPT during quiet respiration rather than at end-expiration as in the LOS, where variation in breath-holding ability is a potent source of error. UOS RPT gives waveforms of consistent shape in each channel and the greater agreement of UOS RPT pressures than SPT pressures recorded simultaneously on the chart and GR800 recorders (Table 4.2, Page 102) indicates that RPT peaks are more easily measured during manual analysis. Where a computer recorder is available, however, maximum tonic UOS SPT pressure is reproducible (Figure 4.8, Page 136), yields detailed information on radial and axial asymmetry (Figure 4.9, Page 131) and allows the study of spontaneous dry swallows. The optimum parameters of UOS tonic pressure in the present study were SPT maximum and mean tonic pressure derived from five or six radially orientated sensors. The GR800 can also be programmed to integrate the area under the pressure curve and it is proposed to compare this measurement of sphincter strength with the average SPT pressure/length index in a future study.

Tonic UOS pressure is reduced with increasing age and in certain types of dysphagia (Chapter 7) but true hypertonicity of the UOS, unlike radiological 'cricopharyngeal spasm', is extremely rare. Of 380 volunteers and patients studied to date, only three had manometric evidence of UOS hypertonicity. Two had lower oesophageal distension (caused by scleroderma and LOS achalasia) with probable reflex increase in UOS tone. The remaining patient was an extremely anxious male with globus sensation whose UOS pressure may have been spuriously high because of his agitation during the test (Cook et al 1987). This suggests that the manometric criteria for cricopharyngeal myotomy should incorporate parameters other than UOS tonic pressure.

The studies of normal deglutition have clarified some areas of UOS physiology which have remained doubtful since the identification by Magendie (1823) of the pharyngo-oesophageal phase of swallowing. Areas which require further clarification have also been identified. Mean pharyngeal amplitude was found to be 36 mmHg in 46 volunteers aged under 57 years and 71 mmHg in older volunteers with an associated reduction in wave duration (Table 4.10, Page 177). This study is larger than any previous strain gauge investigation of the healthy pharynx. Previous reports have shown mean pressures in excess of 100 mmHg. The lower mean amplitude in the present study is in part due to the narrow (2.8 mm diameter) of the recording catheter. The pharyngeal sensor was in the distal 1 to 2 cm of the hypopharynx (3 cm above the UOS sensors). Any lesser degree of sensor separation leads to the registration of UOS pressures in the pharyngeal sensor during UOS elevation (as in the patient with oculopharyngeal dystrophy, Section 7.3) while any greater degree of separation compromises the accuracy of assessment of pharyngeal and UOS coordination (W Pelemans, personal communication 1987). Pressures are greater in the distal pharynx (Orlowski et al 1982) and so the recording level is not likely to have affected the results, nor is the performance of the recording system, which had the capacity to record much higher pharyngeal pressures in some patients and volunteers (including the author). A future study is planned to establish pharyngeal pressures at different levels and in different orientations but the present results suggest that studies using thicker catheters in smaller numbers of subjects (Dodds et al 1975, Orlowski et al 1982, Rex et al 1988) have overestimated the normal pharyngeal contraction amplitude.

The group led by McConnel in Atlanta, Georgia, has proposed that the pharyngeal contractions wave is less important than the 'transmitted tongue driving force' which is the pressure transmitted by a bolus to the pharynx from the base of the tongue and is represented manometrically by a shallow upstroke before the pharyngeal peristaltic wave. This is a concept of rather questionable validity except in patients with a pharyngeal palsy or who have undergone total laryngectomy where tongue propulsion assumes an abnormal importance (McConnel 1988). Firstly, the tongue or 'T' wave must be distinguished from pressure artifacts due to UOS elevation. Secondly, as it is transmitted by the bolus, it disappears during dry swallows (Cerenko et al 1989). Thirdly, the principal justifications cited for its use are that the bolus acts as a bridge between the sensor and more proximal structures, and that the problems of longitudinal catheter movement and radial asymmetry are irrelevant because all that is measured is the force applied to the bolus. The same arguments could, however, equally be used to support the disregarding of this passive pressure phenomenon, which is the accepted approach to equivalent phenomena in the distal oesophagus.

The pharyngeal contraction wave is of increased amplitude and duration during swallows of different foods (Figure 4.13, Page 165 and Figure 4.14, Page 166). Atkinson et al (1957) observed increased contraction amplitude during bread swallows but there has since been only one other detailed study of food swallows (Castell et al 1988). Ramsey et al (1955) found radiological evidence for a more powerful pharyngeal contraction during bread swallows and Lund (1965b) demonstrated a greater degree of cricoid movement radiologically when large boluses were swallowed. Cerenko et al (1989) claim that the pharyngeal clearing force is a small pressure rise after the 'T' wave but preceding the pharyngeal peristaltic wave, whereas Ramsey's studies showed that it was the pharyngeal contraction wave which cleared the laryngeal vestibule. Cerenko's theory that the pharyngeal wave occurs in an empty lumen may be true of single swallows of barium during manofluorometry but takes no account of the presence of double or multiple swallows during normal eating. Mousse, a tenacious semisolid, was frequently swallowed in double complexes, despite being given in 5 ml boluses, suggesting that pharyngeal clearance by a single swallow may be the exception rather than the rule during eating. An upper oesophageal wave is not generated in response to every swallow (Figure 7.2, Page 285) and Ramsey's studies of multiple swallow sequences showed that it was the last wave which cleared the laryngeal vestibule. Given the importance of aspiration in dysphagia (McIntosh et al 1987), the pharyngeal wave appears to be of considerable importance during normal swallowing.

The results of the mousse and bread swallow studies also indicate that deglutition patterns are not, as was previously believed (Bosma 1957, Weisbrodt 1976), under purely central control but are subject to peripheral modification by bolus properties. The advent of microcomputers for use during ambulatory motility studies offers exciting possibilities for the study of unrestricted swallowing while eating a meal and may greatly increase the availability of manofluorometry. The high sample rate required for UOS manometry would rapidly saturate the currently available memory store, however, and an automated analysis programme would be required to analyse the very large number of swallows generated. Automated analysis also allows the derivation of very large numbers of swallow parameters - 15 were used by Castell et al (1988) and 31 by McConnel et al (1988a) but the clinical relevance of these remains to be established. The relative importance of bolus consistency and bolus size (Lund 1965b, Kahrilas 1988a, Cook et al 1988a and 1988b) also remains unknown, but it is evident that swallowing is not a simple all-or-nothing reflex. Nonetheless, it is possible that each individual has a 'preset' normal pattern of deglutition (Ekberg and Nylander 1982a). This pattern, if present, must be subject to alteration with increasing age which results in an increase in pharyngeal contraction, a fall in UOS tone and in a reduced duration and increased velocity of the pharyngo-oesophageal waves. In normal females the UOS after-contraction is significantly increased for water swallows, but this sex difference is absent during bread swallows owing to the relatively greater increase in pressure in males between water and bread swallows. This may imply either that females are less 'bolus-sensitive' than males or that the high pressure generated for water swallows in females is also sufficient for solid bolus propulsion. In either event the similar bread swallow pressure in the two sexes seems to rule out the obvious explanation for the greater female water swallow pressure - namely that there is a smaller available space for bolus passage requiring a greater propulsive force, although the possible manometric effects of the bolus itself also have to be borne in mind. The correlation coefficients of motility parameters during swallows of different substances (Table 4.9, Page 164) tends to support the concept of a 'preset' pattern, yet there is a considerable intrasubject variability in water swallow parameters (Table 4.8, Page 136). This variability may well be reduced, however, by the study of large numbers of swallows with an automated analysis programme.

The UOS deglutition pattern remains the most technically problematic area of UOS manometry. The magnitude of UOS relaxation, its duration and the degree to which it encompasses pharyngeal contraction (in part dependent on the substance swallowed and the degree of separation of the recording sensors) have yet to be fully defined. Different workers have selected the period of minimum relaxation (Kahrilas et al 1988a), the period below 50% of UOS baseline pressure (Castell et al 1988) or the period below 20 mHg or 40 mmHg above the minimum pressure (Rex et al 1988) as the relaxation interval. McConnel's group continues to report markedly negative UOS relaxation pressures and to support the hypopharyngeal suction pump of Barclay (1934), while others report mimimum pressures no lower than intraoesophageal pressure, as originally described by Atkinson et al (1957). There appears to be general agreement with the finding of the present study, however, that UOS residual pressure is influenced by the nature of the swallowed bolus (Castell et al 1988, Cerenko et al (1989). Whether this is secondary to differences in catheter movement is not clear, and indeed it could be argued that it is in some ways artificial to attempt to exclude movements effects, including the 'E' wave, as it is the movement of both the sphincter and the bolus which allows swallowing to proceed normally. The finding of a mean positive residual pressure during swallows of water, bread and mousse (Figure 4.13, Page 165) was felt to indicate a lesser degree of sphincter-on-catheter movement by the use of the narrow diameter Gaeltec assembly, but this interpretation requires manofluorometric confirmation.

The finding that chronic lower oesophageal acid exposure has no significant effect on any parameter of UOS function (Section 5.1) confirms previous reports of the lack of association of GOR on UOS function, but the results of the acute acid exposure studies (Section 5.2) find a parallel only in two recent preliminary reports (Anvari et al 1988, Vakil et al 1988). The report on the laryngeal effects of oesophageal acid is much the largest study of posterior laryngitis using pH monitoring, and the first to combine the technique with examination of posterior laryngeal biopsies. The findings on interarytenoid biopsy suggest that the normal epithelium in the age-range studied is of the stratified squamous type as, although there were no control biopsies, no specimen had epithelium of the respiratory type. There was no characteristic pH monitoring or histological finding in the 17.5% of patients with reflux-associated laryngitis (Figures 5.3 to 5.6, Pages 203 to 206). The presence of somewhat reduced UOS tonic pressure and the low incidence of cigarette smokers in this group tended to support the existence of 'acid laryngitis' as a distinct entity. Previous studies have reported a much higher incidence of this condition (Wiener at al 1986a and 1986b, Katz et al 1988) but these studies were influenced by the lack of histological confirmation, the small numbers and heterogeneous nature of the patients studied and perhaps also by the method of pH data analysis as a high incidence of normal distal oesophageal epithelium was also present. Posterior laryngeal biopsy abnormalities were also associated with cigarette smoking (Table 5.4, Page 208) but the changes were of obscure aetiology in 11 of the 41 patients (27%) idientified.

A 10 year review of the oesophagoscopy performed in the ENT unit of a local district general hospital indicated a 71% incidence of normal findings overall (Table 6.1, Page 217) and highlighted the importance of globus sensation as an indication for the procedure in ENT practice. This led to the setting up of a special clinic for the investigation of globus patients and an attempt to elucidate the aetiological factors of globus sensation. The initial investigations were broadly based in view of the multitude of previously proposed causes of globus. The sex incidence in 207 patients was found to be equal in the third decade, with an average female to male ratio of 3:1 thereafter (Figure 6.1, Page 226), in contrast to the report of an equal sex incidence over the age of 50 years (Moloy and Charter 1982). No evidence was found to support vitamin deficiency, tonsillitis, sinusitis, spondylitis or thyroid deficiency as a frequent cause of globus sensation. The results of an investigation of 87 patients by prolonged ambulatory pH monitoring showed a 23% incidence of prolonged total AET compared with controls (Figure 6.2, Page 233). Even allowing for a 5% false negative rate on the basis of concomitant oesophageal biopsy, abnormal GOR was associated with globus in only 28% of patients. The results also confirmed the wide range of AETs in healthy subjects which has been described recently by Schlesinger et al (1985), Shaker et al (1988b) and Smout et al (1988) and which shows a positive skew in the data distribution, requiring analysis by non-parametric methods. The only other worker to use pH monitoring in globus patients (Batch 1988) performed the test in fewer than one quarter of patients, used an arbitrary upper limit of normal acid exposure times and appeared to discount a 69% incidence of normal oesophageal biopsy findings. It seems that abnormal degrees of GOR are present in around 30% of globus patients but that reflux is within physiological limits in the majority. Furthermore, the majority of patients with symptomatic reflux do not experience globus sensation (Thompson and Heaton 1982).

A total of 165 globus patients underwent upper oesophageal manometry and the results constitute a major contribution to the understanding of the aetiology of globus sensation as previous manometric studies had been performed in only 9 to 18 globus patients. With the exception of two patients, there was no evidence of UOS hypertonicity (Watson and Sullivan 1974) or mid-oesophageal dysmotility (Flores et al 1981, Linsell et al 1987). Detailed analysis of deglutition patterns in 83 globus patients studied with the strain gauge assembly showed significant increases in pharyngeal and UOS after-contraction pressures compared with the 67 volunteers (Figure 6.3, Page 244). The globus patients had a reduced swallow duration and the resultant rapid, hypertonic swallow pattern is represented schematically in Fgure 6.4 (Page 246). McConnel et al (1988b) observed high amplitude pharyngeal contractions in their only globus patient studied by manofluorometry. The patient, a 39 year old woman, was thought to be suffering from a neurological disorder but the outcome of neurological referral was not stated.

The increase in after-contraction pressure compared with normal subjects was relatively greater in male patients, because of the lower normal after-contraction pressure in males. The results of the study are of great interest because the finding of higher UOS after-contractions pressure in normal females suggests that women may be 'physiologically closer' to the development of globus sensation than men. This provides the first credible explanation for the sex incidence of globus other than the greater propensity of females to minor psychological disorders. The fact that males with globus seem to generate a relatively greater increase in after-contraction pressure prior to the development of globus sensation may also explain why male patients have been found to be more refractory to treatment than females (Mair et al 1973). Furthermore, although it remains possible that the pharyngo-oesophageal dysmotility may arise as a consequence of globus sensation, it is also possible that the motor abnormality represents a conversion phenomenon, explaining why patients develop globus rather than other functional symptoms, eg dyspepsia, tinnitus or dizziness.

The results also include the largest psychological study of globus patients to date, which is somewhat surprising in view of the prevalence of globus and its historical associations with hysteria. The classical concept of 'globus hystericus' proved an obstacle to the understanding of globus until the 18th century when the first organic explanations were proposed. Ironically, it was the exclusive focus of subsequent attention on the organic aetiological theories which restricted the understanding of globus in the 20th century. The present results show that female globus patients are introverted and have increased levels of free floating anxiety, depression and somatic concern (Figure 6.5, Page 257). These factors are likely to antedate the development of disease (Robertson et al 1987) and may contribute to a vicious circle of rapid, hypertonic swallowing in association with heightened awareness of bodily sensation (somatisation). In respect of diagnostic classification, the category of the somatoform disorders which globus is most likely to represent appears to be that of conversion disorder (Diagnostic and Statistical Manual 1980). This is supported not only by the results of the present psychological studies but also by the presence of an abnormality of motor function at the location of the symptom and by the finding (Othmer and DeSousa 1985) that globus is the fourth most discriminating symptom of conversion disorder. To some extent, therefore, the results of this unique investigation into the aetiology of globus sensation have turned late 20th century attention back to the original 'globus hystericus' but with a greater insight into the physical and psychological mechanisms of the generation of globus and with correspondingly better prospects for the development of an appropriate management policy.

Finally, three categories of normal pharyngo-oesophageal dysmotility were investigated (Chapter 7). The ability of the Gaeltec catheter and GR800 recorder to demonstrate subtle but consistent alterations in the timing of deglutition after laryngeal irradiation in asymptomatic patients is a testament to the sensitivity of the recording methods and has led to a further study to confirm the proposal that the motor abnormalities present may, like those demonstrated in the irradiated rectum (Varma et al 1985 and 1986), be due to radiation-induced changes in the myenteric plexus. The majority of patients with functional cervical dysphagia were elderly males but there was a very wide age-range and a variety of associated symptoms (Table 7.1, Page 271). The greatest degree of manometric abnormality was present in patients whose cervical dysphagia was associated with choking episodes who had an increase in peristaltic amplitude and pharyngeal wave duration, with a reduction in UOS pressure/length index. Despite the distressing nature of the symptom in many patients, manometric evaluation was otherwise remarkably normal, but it is possible that the study of larger numbers of patients with each clinical variant of cervical dysphagia may yield some abnormal findings. It is also proposed to continue to recruit pharyngeal pouch patients for study, but the tendency for the catheter to become coiled in the pouch may limit the success of this investigation.

Much of the manometric abnormality demonstrated in the 14 patients with dysphagia of neuromuscular origin (Figure 7.1, Page 283) was due to the inclusion of six patients with unilateral vagal paralysis, although the young male with oculopharyngeal dystrophy demonstrated gross incoordination of pharyngo-oesophageal events during bread swallows. A similar abnormality was observed in a female patient with postoperative dysphagia. Both patients had normal coordination of water swallow events, a finding which supports the continued use of bread swallow studies in the assessment of patients with dysphagia. Unilateral vocal cord palsy was found to be associated with significant reductions in UOS after-contraction pressures, pharyngeal pressure and a trend to reduced mean tonic UOS pressure and reduced UOS pressure/length index but unilateral vagal paralysis in this small sample did not appear to alter lower oesophageal function significantly. This suggests that bilateral vagal innervation may be more important for the normal function in the pharyngo-oesophageal segment than in the distal oesophageal segment.

These preliminary findings require to be validated in a larger sample, and a systematic comparison of the manometric effects of recurrent laryngeal nerve and of high vagal paralysis is planned, as a lesion confined to the former produces no abnormality of function radiologically (Lund and Ardran 1964). Lund (1965a) also demonstrated the absence of a separate vagal branch to the cricopharyngeus muscle in man but much of the remaining work on the neural control of deglutition has been performed in experimental animals. Before manometric evaluation can delineate syndromes of neurological dysphagia, there is a need to return to the dissecting-room and to identify the precise distribution of the human pharyngeal plexus. 'In my end is my beginning'.

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9.2 PRESENTATIONS

Some of the results documented in this thesis have been presented at the meetings listed below.

Rigid endoscopy in ENT practice.
Wilson J A, Murray J A M, Von Haacke N P.
Scottish Otolaryngological Society, Crieff, June 1986
Abstract: Clin Otolaryngol **12**:153, 1987

Globus sensation and reflux - a study with ambulatory pH monitoring. Wilson J A, Pryde A, Heading R C.
British Society of Gastroenterology, Cardiff, Sept 1986.
Abstract: Gut **17**:A1242-1243, 1986

Globus and gastro-oesophageal reflux.
Wilson J A, Pryde A, Heading R C, Maran A G D.
Otolaryngological Research Society, Bradford, April 1987 and British Academic Otolaryngological Conference, Glasgow, July 1987
Abstract: Clin Otolaryngol **13**:79, 1988

Laryngitis and acid reflux: an ambulatory pH study.
Wilson J A, White A, von Haacke N P, Heading R C, Pryde A, Piris J, Maran A G D. Otolaryngological Research Society, London, Oct 1987
Abstract: Clin Otolaryngol (in press)

Posterior laryngitis and acid reflux.
Wilson J A, Pryde A, White A, von Haacke N P, Maran A G D, Piris J.
American Gastroenterological Association, New Orleans, May 1988.
Abstract: Gastroenterology **94**:A498, 1988

Normal UOS: A baseline for measurement of cricopharyngeal dysfunction. Wilson J A. British Society of Gastroenterology Oesophageal Section Symposium, Manchester, May 1988

The effect of acid on upper oesophageal sphincter pressure (UOSP). Wilson J A, Pryde A, Heading R C.
XIIIth International Congress of Gastroenterology, Rome, Sept 1988.
Abstract: Gastroenterol Internat **1**, Suppl 1: Abstract 63, 1988

Upper oesophageal sphincter dysfunction in globus pharyngis.
Wilson J A, Pryde A, Heading R C.
Otolaryngologic Research Society, London, Oct 1988
Abstract: Clin Otolaryngol (in press)

Globus pharyngis. Wilson J A.
Midland ENT Forum, Birmingham, Dec 1988

Normal upper oesophageal sphincter motility.
Wilson J A, Pryde A, Heading R C.
Caledonian Society of Gastroenterology, Edinburgh Feb 1989

9.3 PUBLICATIONS

Publications relating to this thesis are listed below.

Rigid endoscopy in ENT practice. Wilson J A, von Haacke N P, Murray J A M. J Laryngol Otol **101**:286-292, 1987

Globus sensation is not caused by gastro-oesophageal reflux. Wilson J A, Heading R C, Maran A G D, Pryde A, Piris J, Allan P L. Clin Otolaryngol **12**:271-275, 1987

Is globus hystericus? Wilson J A, Deary I J, Maran A G D. Br J Psychiatry **153**:335-339, 1988

Gastroesophageal reflux and posterior laryngitis. Wilson J A, White A, von Haacke N P, Maran A G D, Heading R C, Pryde A, Piris J. Ann Otol Rhinol Laryngol (in press)

Pharyngoesophageal dysmotility in globus sensation. Wilson J A, Pryde A, Piris J, Allan P L, Maran A G D, Heading R C, Macintyre C C A. Arch Otolaryngol Head Neck Surg (in press)

Covert psychiatric disturbance in patients with globus pharyngis. Deary I J, Wilson J A, Mitchell A, Marshall T. Br J Med Psychol (in press)

Published abstracts are listed with the associated presentations in Section 9:2.